Primary Hypertension in Children

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Abstract

Primary hypertension in children is not as common as in adults; recent studies suggest a prevalence of 3–4 % in the pediatric population. However, more recent reports have highlighted an increasing prevalence of HTN and prehypertension, likely due to childhood obesity. Given the global burden of hypertension, identification and management of primary HTN is beneficial to the individual child and has important implications for society as well, particularly since tracking studies have established that adult primary HTN has its antecedents during childhood. Studies are limited on the pathophysiology of primary HTN in children; however, evidence suggests that the proposed multifactorial and complex genetic, environmental, and biological interactions involved in the development of hypertension in adults provide a basis to understand HTN in children as well. Primary HTN in young children is a diagnosis of exclusion, and selective workup is needed to rule out any underlying secondary causes; however, in adolescents, primary hypertension is much more common than secondary hypertension. Early identification and management of elevated BP in the pediatric population is important to decrease the risks for end-organ injury in both the pediatric and adult population.

Keywords

Primary hypertension • Children • Hypertension pathophysiology

Introduction

The diagnosis of hypertension accounts for 58–65 million hypertensive adults in the United States alone and is also the most common diagnosis for outpatient physician visits and prescription drugs [1, 2]. Primary HTN is believed to have its antecedents during childhood. Studies

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have shown that the relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis [3]. Therefore, it is important that those providing care to children approach the issue of HTN both as a societal challenge and as a disease affecting discrete individuals.

Prevalence

Primary hypertension is prevalent in 29–31 % of the adult US population and nearly 44 % of the adults in Europe [4]. It is difficult to estimate the worldwide prevalence of pediatric HTN due to regional differences in definition and normative values used to diagnose hypertension. In the United States, recent screening studies and survey data have given an estimated prevalence of 3–4 % [5–8] in the pediatric population.

More recent reports have highlighted the effects of childhood obesity on the prevalence of HTN and prehypertension in children and adolescents [8, 9]. The frequency of hypertension appears to increase as the severity of obesity increases. The effects of obesity on childhood hypertension are highlighted in publications of case series of children referred to tertiary centers, in whom up to 91 % are now found to have primary HTN [9, 10].

Incidence

Data on the incidence of HTN in children are scarce. The analysis of the National Childhood Blood Pressure database (BP recorded at 2- and 4-year intervals) has shown an incidence rate of 7 % per year in adolescents with prehypertension. However, the diagnosis of hypertension was based on single BP readings, which is not consistent with current guidelines.

More recent data from Redwine et al. in nearly 1,000 adolescents [11] has reported an incidence rate of 0.7 % per year for hypertension diagnosed according to recommended guidelines. In adolescents who were prehypertensive at the initial screening, the rate was 1.1 % per year as compared to a rate of 0.3 % per year in adolescents who were normotensive at the initial screening. The highest risk for progression at 6.6 % per year was seen in adolescents with elevated BP at all three visits. As highlighted in a recent review [12], these findings could potentially translate into nearly half a million hypertensive adolescents after 5 years.

Predictors of Primary Hypertension

BP tracking refers to the stability of repeated BP measurements over a period of time; thus, if tracking is present, children with elevated BP are more likely to become hypertensive as adults. Increased strength of tracking is reported in the presence of a family history of HTN, increased body weight, or increased left ventricular mass [13–16]. This is indicative of the interaction between the genetic and environmental factors influencing BP. The Muscatine Study, for example, has demonstrated that primary HTN in young adults has much of its origin during the childhood years [17]. Although the strength of the tracking phenomenon has been questioned [18], tracking studies are important as they underscore the need for early identification and treatment of elevated BP, given the current global scenario of increased cardiovascular disease-associated morbidity along with the worldwide increase in childhood and adult obesity. An analysis from the Fels Longitudinal Study [19] (non-Hispanic whites only) has reported that the earliest differences in systolic BP occurred at 5 years of age in boys and 8 years of age in girls. The BP cutoffs (boys < 102/65 girls < 92/62 at 5 years, boys < 104/64 girls < 102/64 at 14 years, boys < 115/67 girls < 104/64 at 18 years) as developed by the random effects model in the analysis are lower than the 50th percentile and therefore not considered high risk per the current Fourth Task Force Report recommendations [20]. Systolic and not diastolic BP above the cutoff values as reported in the study was associated with increased risk for developing hypertension with or without the metabolic syndrome [19].

Definitions and Techniques

Criteria for making a diagnosis of primary HTN are summarized in Table 20.1. As per the current recommendations, BP readings of more than 95th percentile for sex, age, and height on three separate occasions are required for diagnosing HTN. The most widely used nomograms for BP in children are those provided in the Fourth Task Force Report on Blood Pressure in Children and Adolescents [20].

According to the recommendations of the Fourth Task Force Report, pediatric HTN is now categorized into pre-HTN (SBP or DBP between the 90th and 95th percentile or greater than 120/80 in adolescents), stage 1 HTN (SBP or DBP ≥95th percentile up to the 99th percentile plus 5 mmHg), and stage 2 HTN (SBP or DBP >99th percentile plus 5 mmHg). Children and adolescents with primary hypertension may present with either stage 1 or stage 2 HTN [10, 21]

Primary HTN in children is often associated with a family history of HTN or other cardiovascular disease. Other comorbid conditions associated with primary HTN in children, which increase the risk for cardiovascular disease, include abnormal lipid profile, glucose intolerance, and sleep abnormalities.

Some researchers have questioned the validity of the current definition of HTN in children [4]. HTN is defined by a statistical cut point in the continuum of BP nomograms derived from different epidemiologic studies using a rigorous study protocol [5, 20, 22]. The definition of HTN is concurrent with an increased risk of recognizable morbidity and mortality that becomes increasingly prevalent as BP increases. A pragmatic definition of HTN would be the level of systolic BP and/or diastolic BP above which recognizable morbidity (such as stroke, heart failure, or chronic renal failure) occurs. As of this writing, there are no data that adequately define this in children. This is in contrast to adults, where in outcomes data in terms of increased cardiovascular morbidity or mortality is used to define normal versus elevated BP.

As reviewed by Collins et al. [4] the recommendation of using three BP readings to diagnose HTN may in fact underdiagnose HTN in children. Currently there is no data to demonstrate that 2 BP readings are better or inferior in identifying hypertensive children. The same review [4] also highlights the limitations of using the statistical definition of HTN for minority ethnic groups, such as African Americans, who may have a higher prevalence of HTN and associated end-organ damage. The use of Gaussian distribution curves would diagnose HTN at much higher levels in these groups and possibly delay indicated interventions [4]. However as reviewed by Flynn et al. [23] the fundamental question that remains unanswered is what BP is nonphysiological and whether this represents an absolute value or a percentile cutoff.

The importance of obtaining accurate BP readings in diagnosing hypertension has been emphasized repeatedly by consensus organizations [20, 22]. There are many confounding factors in BP measurement in children, including cuff size, the number of measurements, type of instruments used, patient position (supine or sitting), and the choice of sound [Korotkoff (K) 4 vs. K 5] used for defining diastolic BP [20]. Many of these issues are discussed in detail in Chap. 9.

Table 20.1 Criteria to use in diagnosing primary HTN in children

Primary criteria
➢ An average of 2–3 readings of systolic BP and/or diastolic BP exceeding the 95th percentile for age, gender, and height repeated three times over a 2–3-month period
➢ Ambulatory blood pressure measurements over a 24-h period that exceed the 95th percentile for age-matched controls and/or a failure to find a nocturnal dip
➢ Unable to identify a known secondary cause of HTN
Supportive criteria
➢ Stage 1 HTN on presentation
➢ Children obese on presentation (BMI > 95th percentile)
➢ Family history of HTN
➢ Idiopathic HTN associated with high, normal, or low PRA
➢ Abnormal response to mental stress
➢ Evidence of end-organ effect; funduscopic changes, cardiac enlargement by electrocardiogram and/or echocardiogram (suggestive of long-standing HTN)

Ambulatory blood pressure monitoring (ABPM) has been used increasingly to diagnose HTN, define diurnal BP variability in normal and hypertensive populations (including children) [24], and to evaluate therapy. ABPM overcomes many of the measurement issues associated with office BP measurement, is essential for diagnosing white-coat HTN, and may sometimes help to distinguish primary versus secondary HTN in children [25]. ABPM is discussed in depth in Chap. 11.

BP Homeostasis and Pathophysiology of Hypertension

The wide variety of factors involved in regulating blood pressure are discussed in detail in an earlier section of this text and have been reviewed in detail elsewhere [26, 27]. A brief overview of the factors determining BP is presented here, however, as it is necessary to understand the steps involved in the generation and persistence of primary HTN (Table 20.2). Due to paucity of pediatric studies, most of the discussions below are based on adults and animal studies. However evidence from tracking studies suggests that the proposed multifactorial and complex genetic, environmental, and biological interactions involved in development of hypertension in adults would provide a basis to understand HTN in children as well.

HTN occurs when the sum of cardiac output (CO) and total peripheral resistance (TPR) increases. The factors involved in increasing BP during the generation and maintenance of primary HTN are often different. In one form, the increase in CO during its early stages has been attributed to a hyperkinetic circulation characterized by increased heart rate (HR), cardiac index and forearm blood flow secondary to increased sympathetic tone, and cardiac contractility [28, 29]. Fixed persistent primary HTN is characterized by an increase in TPR and a return to a normal CO. In the second form, early HTN is characterized by increased left ventricular (LV) mass, as also reported in normotensive offspring of hypertensive parents. These observations raise the possibility that repeated neural stimulation and upregulation of cardiac receptors may be the primary event in the onset of primary HTN [30]. The observed changes, from that of an increased to normal CO, and an increased TPR over time enable a constant blood flow to organs in experimental animals and humans. The presence of functional versus irreversible structural changes explains response to therapy and the potential reversibility of the hypertensive process aggravated by obesity, stress, and/or excessive salt intake.

Table 20.2 The basic blood pressure formula and its physiologic transformation to HTN

1. Pressure equals flow times resistance
2. BP = volume times resistance
3. BP = CO times total peripheral resistance
4. BP = flow (preload + contractility) x resistance (arteriolar functional contraction + vessel anatomical changes), for example, BP = flow x resistance
5. HTN = a net increase in CO and/or increased peripheral resistance

Kidneys maintain intravascular volume by regulating sodium and water excretion and subsequently are the primary influence on the long-term control of BP. The two main renal mechanisms involved are *pressure natriuresis* (volume) and the *renin-angiotensin-aldosterone system* (*RAAS*) (vasoconstriction). Each mechanism, in turn, is influenced by multiple other factors which may increase or decrease the relative contribution of volume and/or vasoconstrictor components of BP. *Pressure natriuresis* is the increased urinary excretion of salt and water in response to elevated arterial pressure to maintain BP by regulating body volume. Despite the wide variations in sodium intake, the kidneys through a tightly regulated balance of glomerular filtration and tubular secretion/absorption are able to maintain a constant BP. RAAS influences both elements of the BP formula. Renin is secreted by the juxtaglomerular cells of the kidney in response to physiological and nonphysiological reduction in BP, renal blood flow, and sodium chloride load at macula densa. ANG II is the effector arm of the RAAS and it increases vascular contractility and thereby peripheral resistance by binding to AT1 receptors present on the vascular smooth muscle. ANG II

binding within the adrenal gland leads to increased aldosterone production, sodium retention by the kidney, and volume expansion. The AT2 receptor, which is not involved in the vascular/smooth muscle contraction, is known to play a role in cell differentiation and hypertrophy. The central role of the RAAS in hypertension has recently been reviewed elsewhere [31].

Genetic renal defects linked with *abnormal sodium homeostasis* in primary HTN include increased efferent arteriolar tone leading to increased sodium reabsorption, congenital reduction in the number of nephrons and filtering surface [32], nephron heterogeneity [33], and non-modulation that involves abnormal adrenal and renal responses to angiotensin (ANG) II infusions [34]. Single-gene disorders that affect renal sodium handling are discussed in more detail in Chap. 6.

Recent research in animal models has highlighted the role of medullary circulation in pressure natriuresis and pathogenesis of hypertension [35]. Increased medullary blood flow is associated with increase in vasa recta capillary pressure, loss of osmotic gradient, and thus increased natriuresis. Blunting of the pressure natriuresis due to alteration of the balance between medullary vasodilators (nitric oxide, endothelin) and medullary vasoconstrictors (vasopressin and angiotensin II) has been linked to HTN [35].

Nephron heterogeneity [33] has also been proposed as an underlying mechanism for blunted natriuresis in hypertensive patients. The heterogeneity is attributed to a smaller group of ischemic nephrons with markedly increased renin secretion leading to angiotensin II-mediated arteriolar constriction and vascular remodeling. This is supported by reports of focal afferent arteriolar narrowing (common) along with juxtaglomerular cell hyperplasia associated with increased renin secretion in patients with primary hypertension.

Eutrophic vascular remodeling [36] is the pathologic alteration of the precapillary resistance vessels characterized by a reduction in the vessel lumen associated with increase in media to lumen ratio without in the vessel-media cross section. This vascular remodeling is increasingly identified as the predominant change in hypertensive patients and attributed to multiple factors such as increased (a) myogenic tone of the vessel wall, (b) matrix deposition, and (c) growth towards the vessel lumen with apoptosis in the periphery and altered smooth muscle motility of the vessel wall [36, 37]. RAAS through ANG II appears to be significantly involved in the vascular remodeling as evidenced by animal studies and human studies reporting improvement in small arterial function with ACE/ARB and not other antihypertensives [27, 36, 37].

Laragh et al. have proposed that patients with primary HTN can be divided into three groups: normo-, hyper-, and hyporeninemic based on *renin profiling*, for example, the comparison of plasma renin activity (PRA) to sodium excretion [27, 38]. This group concluded that high-renin primary HTN patients are at greater risk for vaso-occlusive events such as stroke, infarction, and renal failure, while those with low-renin primary HTN are volume overexpanded and less likely to experience the aforementioned end-organ damage. Moreover, they suggest that drug therapy should be targeted at the underlying primary pathophysiology, and renin inhibitors and diuretics be, respectively, used to treat patients with high- and low-renin primary HTN. Limited studies in children have included renin profiling and the incidence of low-renin HTN is estimated at 19 % [39]. There is currently no long-term data on the outcome of hypertensive children, who were renin profiled at diagnosis. Studies have also shown that PRA is higher in those with high uric acid levels and inversely related to fractional excretion of uric acid in hypertensive patients [40]. This suggests the presence of altered glomerulotubular balance in hypertensive patients. Feig et al. have recently reported that hyperuricemia (uric acid >5.5 mg/dl) is more commonly associated with primary HTN compared to secondary or white-coat HTN [41].

Sympathetic nervous system (SNS) activity can function as an initiator and as a secondary contributing factor for elevated BP. Stress and/or a primary catecholamine regulation defect in the brain may directly cause vascular vasoconstriction. SNS stimuli from the vasomotor center activate efferent pathways causing norepinephrine

release at peripheral nerve endings, which in turn stimulate adrenergic receptors. Circulating epinephrine derived from the adrenal medulla can stimulate norepinephrine release through stimulation of presynaptic β-2 receptors. Excessive circulating catecholamines increase the BP response to a sodium load. Baroreceptor reflex arc dysfunction occurs in some patients with primary HTN. Usually, elevated BP leads to reflex lowering of the BP by reducing sympathetic outflow from vasomotor centers and increasing vagal tone. The responsiveness of this system resets itself to a higher level with BP elevations and plays a role in the persistence of HTN. Impaired circulatory homeostasis and vascular reactivity in hypertensive patients in comparison to normotensives as indicated by increased BP, tachycardia, and flushing in response to noxious stimuli provide evidence for SNS overactivity. Although *dopamine* is a modulator of systemic BP, with additional actions on fluid and sodium intake, no mutations have linked patients' primary HTN or genetic HTN in animal models to the D1 receptor.

Perinatal influences: Critical development period theory proposes developmental stages which are more sensitive to certain environmental factors and thus lead to propagation of certain genetic information. As reviewed by Kunes et al. [42], these changes are not detected immediately but after a certain delay ("late consequences of early alterations"). Barker's hypothesis and subsequent studies provide support for the intrauterine period being a critical period for development of primary HTN (discussed in detail in Chap. 7) [43, 44].

Barker first proposed that HTN in adult life is associated with retarded fetal growth and this relationship becomes stronger as the patient ages [43, 45]. Postulated mechanisms include insulin resistance, exposure of a malnourished fetus to maternal glucocorticoids that alter subsequent steroid sensitivity, as well as the metabolism of placenta cortisol [46], and the presence of a reduced number of glomeruli. The net result is a reduced number of glomeruli (as much as 25 % in experimental animals), a decreased glomerular surface area, and a reduction in glomerular filtration rate (GFR) per nephron [47]. The impaired nephron function eventually leads to HTN. A similar outcome has been reported with the blockage of the RAS with losartan after birth. Studies in rats have shown that young rats are at higher risk for salt-sensitive hypertension compared to older rats, hypertensive response to salt is more marked at young age, and antihypertensive therapy is effective and may have preventive effect on hypertension when started earlier. The identification of similar critical periods in humans could have significant effects on hypertension research [42].

Genetics: At least 25–30 candidate genes have been suggested as contributors to the hypertensive process by affecting critical factors involved in the vasoconstriction and/or volume elements of the BP formula (Table 20.3). Due to its central role in BP regulation, gene polymorphisms of the RAAS system have been frequently evaluated in hypertensive patient cohorts. Current evidence links genes controlling plasma angiotensinogen (AGT) with risk for HTN, while no conclusive association is reported with the ACE gene polymorphisms [48, 49]. Angiotensinogen M235T genotype has been associated with increase in angiotensinogen levels and increased risk for hypertension [49]. The theory of impaired genetic homeostasis postulates [50] that the mismatch between genes involved in the regulation of BP and the acculturated changes in our society accounts for the recent increase in documented HTN. Synchronicity, a process by which growth spurts are associated with increases in BP, may be accelerated in genetically prone hypertensive individuals [51]. Allometric dysfunction, a process by which somatic and renal growths fail to match each other, might lead to HTN if environmental factors enable excessive non-genetically determined growth to occur [52]. The failure of renal vascular remodeling to occur during fetal and postnatal life might alter the expected decreases in the activity of RAS and/or sodium regulatory mechanisms. Premature telomere shortening, a process associated with normal aging, may lead to HTN [53]. Finally, perturbation in neural development of the sympathetic nervous system and/or cardiac β1-receptors may predispose newborns to develop a hyperkinetic circulation and, therefore, HTN [54].

Table 20.3 HTN and gene studies

Genome-wide association study (GWAS)	
Strengths – hypothesis-free studies, lead to discovery of new genes	
Weaknesses – large sample size is needed to detect meaningful association, higher study costs, need for stricter quality control, and handling of large databases	
Linkage reported in most of the chromosomes, however there is little current clinical application	
➢ WTCC [86], Saxena R [87], Levy D [88], Kato N [89], Sabatti C [90] – no significant genome-wide association	
➢ Global BPGen study [91] – 8 regions with genome-wide significance in chromosomes	
➢ CHARGE study[92] – significant genome-wide associations between 13 SNPs with SBP, 20 SNPs with DBP and 10 SNPs with HTN	
Genome search meta-analysis (GSMA) – meta-analysis of the GWAS	
➢ Levy D [82]	Global BPGen and CHARGE meta-analysis 8 SNPs on chromosomes; 12 (ATP2B1), 10 (CYP17A1), 11 (PLEKH7), 12 (SH2B3), 10 (CACNB2), 15 (CSK-ULK3), 12 (TBX3-TBX5), 3 (ULK4) with significant association with SBP/DBP/HTN SNP ATP2B 12q 21–23 associated with significant association with SBP/HTN
➢ Wu X [93]	No locus achieving significant linkages; suggestive linkage at 2p14 and 3p14.1
➢ Koivukoski [94]	Significant association with DBP and HT at 2p12-q22.1, 3p14.1-q12.3
➢ Liu [95]	No genome-wide significant linkage to HTN
Candidate gene analysis	
Strengths – known pathophysiological processes associated with HTN are studied at genetic level, and animal data is available on these genes, compared to GWAS that are low cost	
Weaknesses – HTN is polygenic and individual genetic contribution to HTN phenotype may be small, cannot evaluate gene/environment interaction, and have less chance for identifying newer genetic pathways linked to HTN	
➢ G-protein system [96] – G-protein β3-subunit (GNB3) gene C825T polymorphism, G-protein receptor kinase 4 (GRK4) gene, Gαs subunit (GNAS) gene	
➢ α-Adducin gene (ADD1) gene, Gly460TRP polymorphism[97]	
➢ Polymorphisms of CYBA gene encoding p22 phos subunit of the NADPH oxidase system[98]	
➢ Renal sodium transporters[99]; SCNN1B gene encoding β-subunit of ENaC transporter β-ENaC G589s polymorphism, SLC9A3 gene encoding NHE 3 exchanger in proximal tubule	
➢ RAAS genes[100, 101]: (1) AGT gene for angiotensinogen M235T, A-6G, A-20C polymorphisms, (2) ACE deletion/insertion (D/I) polymorphism intron 16 and ACE 2 gene, (3) type 1 angiotensinogen II receptor gene (AT1R), (4) CYP11B2 aldosterone synthase gene C344T polymorphism	
➢ Genes linked with changes in vascular tone [102]; a*drenergic receptors*; (1) α1a gene 347 Cys polymorphism, (2) α2a gene Dral polymorphism, (3) α2b gene Glu 301–303 deletion variant, (4) α2c insertion/deletion polymorphism *nitric oxide (NO)* endothelial NO synthase gene on chromosome7 G849T polymorphism	
➢ *Adenosine monophosphate deaminase (AMP)* AMP-1 (AMPD 1) gene polymorphism *endothelin* 1 gene polymorphisms and G-protein polymorphisms	
➢ Mitochondrial gene mutations[99, 103]; mitochondrial NADH dehydrogenase 3 gene A10398G mutation	
Large-scale candidate gene studies	
➢ Sober S [104], Padmanabhan S [105], Tomaszweski M [106] – no significant association with BP candidate genes	
➢ Johnson T [107] replicated SNP for angiotensin locus AGT and ATP2B1 locus of other studies and reported other novel loci	

Risk Factors Involved in Childhood Primary HTN

Age and Gender

Children have lower BP levels in comparison to adults, but the levels progressively increase with age, with a linear rise from 1 to 13 years. This increase is related more to body size than age. Primary HTN is the most common cause of HTN in older children especially in the postpubertal group. The prevalence of HTN and pre-HTN is greater in boys than girls [55]. Also, in girls BP rises rapidly between 6 and 11 years as compared to 12–17 years, while the opposite is seen in boys [56]. The male preponderance of high BP persists

till 50 years of age, when BP levels in women again exceed men's [56].

Race and Ethnicity

The prevalence of primary HTN is clearly influenced by race and ethnicity [57]. Native Americans have the same or higher rate of primary HTN as Hispanics who have the same or lower BP than Caucasians. The prevalence of HTN in blacks is twice that of whites, has an earlier onset, and is associated with more end-organ damage. These differences are most likely quantitative [58] for the characteristics of the hypertensive process are similar in blacks and whites when corrected for age, cardiovascular and renal damage, and level of BP [59]. Blacks have higher sleep and less dipping in their nighttime ABPM values than age-matched whites [60]. Blacks experience a greater degree of renal global, segmental, and interstitial sclerosis than whites at an earlier age, despite having similar BP and degrees of proteinuria [61, 62].

Genetics and Family History

Up to 40 % of HTN is attributable to genetic factors indicating increased risk for hypertension in genetically related individuals [63]. However, it is important to note that the interaction between genes and a permissive environment is essential for the development of elevated BP. Genome-wide association study (GWAS) has identified the association between common/new genetic variants and BP/HTN. The novel insight into disease pathology from these associations has not translated to clinical utility. Such differences may reflect environmental factors, the influence of other genes, evolutionary diversion (race and ethnicity), and study design and/or technical issues (Table 20.3). In the future, individual genetic information will help in early identification of high-risk groups for targeted preventive measures and pharmacotherapy based on individual disease pathways with low risk for adverse effects.

Obesity

Obesity, which is found in 35–50 % of hypertensive adolescents, is one of the most important factors involved in both the generation and persistence of childhood primary HTN [9]. Prevalence studies, including tracking studies of weight change and BP in young adults [64], have reported an increase in childhood obesity and HTN in obese subjects. The relationship between elevated BP and weight begins in early childhood and has been reported to occur as early as 5 years [65]. The Muscatine Study showed that changes in ponderosity over 11 years correlated directly with BP changes [17]. Obesity is associated with the "metabolic syndrome," which is characterized by insulin resistance, an atherogenic dyslipidemia, activation of the sympathetic nervous system, and an increased tendency for thrombosis (see Chap. 19). Other suggested mechanisms of obesity-related HTN include hyperinsulinemia, hyperproinsulinemia, renal sodium retention, increased sympathetic activity [29], increased plasma volume, increased levels of dehydroepiandrosterone [66], and increased CO. Increased plasma aldosterone activity in obese adolescents correlates with increases in their mean BP; the BP level falls when weight loss occurs [67]. Obesity hypertension is discussed in more detail in Chap. 17.

Salt Intake

It is estimated that since the Paleolithic period, the average sodium intake in the human diet has increased almost fivefold to approx 3,400 mg/d, a level sufficiently high enough to enable high-BP expression in salt-sensitive individuals [68]. Also, epidemiologic studies have shown that BP levels are higher in societies with high salt intake with higher BP associated with sodium intake above 100 meq/day [69]. He et al. [70] have reported a nearly 50 % increase in salt intake between the ages of 4 and 18 years. The study also reports significant association between salt intake and systolic BP which is independent of age, sex, body mass index, and dietary potassium.

Table 20.4 Role of sodium in primary HTN

Experimental evidence
➢ High salt intake increases renal vascular vasoconstriction, catecholamine release, and NaK ATPase inhibitor ouabain, which in turn leads to increase in intracellular calcium and sodium
➢ In salt-sensitive patients with essential HTN, BP varies directly with changes in sodium intake
➢ Decrease in salt intake in people with borderline high BP may prevent the onset of HTN
➢ The time and quantity of sodium administration to rats genetically predisposed to HTN determine the onset and level of BP
➢ Similar mother and offspring BP response to sodium restriction supports a genetic predisposition to salt sensitivity
Epidemiologic evidence
➢ Significant correlations between salt intake and BP have been demonstrated in large population studies
➢ Primitive isolated societies with naturally ingesting low-sodium diets do not develop HTN, nor does BP rise with age
➢ Primitive isolated societies increase their BP after being exposed to environments where excess sodium is ingested

Experimental studies (Table 20.4) have shown that the amount and time of introduction of sodium in the diet of newborn rats influences the onset and persistence of HTN. In human neonates, the ingestion of lower sodium (4 meq/L) containing formula after birth was associated with a 2.1-mm/Hg lower BP after 6 months [71]. Even though this difference did not persist a few years later, it is still possible that a life-long effect may be seen.

Approximately 25–50 % of the adult population is considered to be salt sensitive and exhibits increased BP fluctuation in association with slight increase in salt intake. Besides increasing with age, salt sensitivity has been reported in African Americans, obese, metabolic syndrome, and chronic kidney disease patient cohorts. Dietary sodium restriction is a recommendation in all guidelines (national and international) as a component of non-pharmacologic treatment for hypertension. In hypertensive children, the issue of salt restriction has not been fully evaluated in context of their requirements for growth and development.

White-Coat HTN (WCH)

WCH or isolated office HTN is defined as office BP readings ≥95th percentile but with normal values outside the clinical setting. The estimated prevalence of WCH is around 35 % in children being evaluated for persistently elevated casual BP and 44 % in children with a family history of primary HTN [72]. The prevalence of white-coat HTN is higher when the office values reveal borderline or mild HTN and much lower with moderate or severe HTN [73]. Similar to adults, a retrospective study in children has shown that WCH is possibly a prehypertensive condition with increased left ventricular mass and progression to sustained HTN [74]. Increased urinary excretion of cortisol and endothelin in adolescents with WCH identifies a group with distinct metabolic abnormalities [75]. Since urinary endothelin is derived from the kidney, these findings support a dysregulation of renal function. It is possible that WCH in children represents two populations: one that is destined to develop primary HTN (prehypertensive) [76] and one that will remain normotensive outside clinical setting.

Exercise

Exercise provides a number of benefits: increased caloric expenditure, appetite suppression, and improved exercise tolerance. Serum cholesterol and triglyceride levels inversely relate to the level of exercise. Ekelund et al. [77] in their study of nearly 21,000 children reported improvement in cardiometabolic risk factors (waist circumference, fasting insulin, fasting triglycerides and HDL cholesterol, and resting systolic blood pressure) in association with moderate to vigorous physical activity. The improvement in risk factors was regardless of sex and age and also independent of the amount of sedentary activity. WHO's latest guidelines recommend 60 min of at least moderate intensity physical activity in addition to activities of daily living [78]. Andersen et al. in their review of published literature of physical activity and cardiovascular risk factors in children have proposed that physical activity/intervention

of at least 30-min duration, 3 times/week, and intensity sufficient to improve aerobic fitness is sufficient to decrease BP in hypertensive children [78]. Gopinath et al. [79] have recently reported that different sedentary behaviors have a different effect on BP. According to their findings, each hour per day spent in watching TV or playing video games was associated with increase in diastolic BP, while similar time spent in reading was associated with decrease in systolic and diastolic BP. The BP response of hypertensive adolescents to exercise is similar to that of normotensive adolescents, but starts and finishes at higher levels [80]. In adolescents, peak SBP >210 mmHg, and a rise in DBP with dynamic exercise, is occasionally used to determine the need for antihypertensive drug therapy [81].

Lipids and Cigarette Smoking

Prolonged elevation of cholesterol is strongly associated with an increased risk of coronary artery disease. Evaluations of the coronary arteries and aorta of 35 children and young adults dying from noncoronary artery disease events revealed fatty aortic streaks in 61 %, coronary artery fibrous streaks and/or plaques in 85 %, and raised plaques in 25 % [82]. The extent of involvement correlated directly with total cholesterol and low-density lipoprotein (LDL) and, inversely, with the ratio of HDL to LDL cholesterol. Obesity is the most common cause of hypertriglyceridemia, often associated with a low HDL in adolescents. It is well known that inherited disorders of lipid metabolism increase the risk of early cardiovascular disease.

Harmful effects of smoke exposure, active or passive, on the cardiovascular status have been shown in adults [83]. Chronic smoking itself does not increase BP; it is associated with increased cholesterol levels and lower levels of high-density lipoprotein (HDL), which increase the risk of atherogenesis. Simonetti et al. [84] have reported that environmental nicotine exposure as a consequence of parental smoking is associated with increased BP in children as young as 4–5 years of age. The study also reported a synergistic role wherein proportionately progressive increase in BP was noticed in cumulative association with other risk factors such as parental hypertension and obesity.

Stress

Stress of all types can increase BP. When compared to those with normal BP levels, greater increases in sympathetic nervous system and cardiovascular activity occur in offspring of hypertensive parents and in hypertensive individuals. Poverty, sociocultural factors, racial issues, and migration are also known to increase BP. Both SBP and DBP can be correlated with chronic hostility, nervousness, and the demanding perception of environment in adolescents [72]. Type A behavior is associated with increases in SBP, but not DBP [73]. Three models of psychosocial stress that might explain the genesis of primary HTN are the Defense Defeat Model, Demand Control, and Lifestyle Incongruity Index [74]. These models deal with issues such as fight flight, control, aggression, depression, subordination, the relationship between psychologic demands factored by the available latitude of decision-making, and differences between occupational and social class and achievement versus accomplishment.

Conclusions

The increasing diagnosis of primary hypertension in children represents an important shift in our understanding of pediatric hypertension. Primary hypertension in children is a diagnosis of exclusion and children need selective evaluation for any underlying secondary cause. Elevated BP in children is associated with end-organ effects (for a detailed discussion, see Chap. 29). Studies have reported increased prevalence of left ventricular hypertrophy, vascular changes, microalbuminuria, and impaired cognitive function in children with elevated BP [4, 85]. Early identification and management of elevated BP in the pediatric population is important to decrease the risks for end-organ injury.

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