Recent Advances in the Pathogenesis of Hypertension in Children

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Abstract • This commentary discusses current knowledge of the pathogenesis of pediatric hypertension, focusing on the fact that adult health and, to a large extent, adult diseases, are deeply rooted in both hereditary and environmental factors that originate in childhood. Understanding these factors and their pathogenesis not only allows us to appreciate the etiology of pediatric hypertension, but also helps us to target our treatment and better manage the risk factors in the very young that may result in less cardiovascular and kidney disease among adults.

Introduction

The practice of pediatrics has traditionally focused on transient diseases and congenital malformations; thus, a distinct separation between pediatric and adult health issues has been evident in the traditional medical curricula and in subsequent practice. However, it is becoming increasingly clear that adult health and disease and, to a large extent, adult diseases, are deeply rooted in hereditary as well as environmental factors that originate in childhood [1]. An excellent example, from a cardiovascular perspective, is primary hypertension (HT). We should no longer consider primary HT in childhood as an entity separate from adult HT, but rather as a continuum that may have its origins as early as in utero and that persists well into adulthood. The conditions that lead to HT affect not only blood pressure (BP) per se but cardiovascular health altogether. Indeed the current guidelines on BP in children in the U.S. note that primary HT may begin in childhood [1]. However, most HT in children under 12 years of age is secondary and due to causes that range from vascular, to endocrine, genetic, and inflammatory [2].

The most common causes of secondary HT change with age [3], so that while congenital renal and vascular structural and metabolic/endocrine factors are relatively common contributors to the etiology of HT in early infancy and childhood, such diagnoses are less common among hypertensive adolescents and young adults, who more often have acquired renoparenchymal and vascular etiology of their elevated BP. With the rapid increase in childhood obesity [4-5], primary HT, whether in isolation or associated with the metabolic syndrome, is becoming very common in childhood. This commentary is a brief review of the major categories of pediatric HT and their pathophysiologic mechanisms.

Renal Parenchymal Disease

Renovascular Disease

& Renin-Angiotensin-Aldosterone System Mediated Hypertension in Childhood

The physiology of renoparenchymal HT has classically been attributed to both fluid overload and increase in the activity of the renin-angiotensin-aldosterone system (RAS).

In addition, endothelial dysfunction, peripheral and central nervous system activation, among other factors, are now known to be important in leading to HT associated with renoparenchymal disease.

In recent years it has been recognized that the RAS is more complex than was previously thought [6-7]. An important effect of the circulating RAS is to increase sodium and water retention, primarily through the actions of aldosterone on the renal distal tubule, as well as...
through the direct mechanism of angiotensin II, the octapeptide that is one of the most potent known vasoconstrictors. In addition to a circulating RAS, there are multiple tissue renin-angiotensin systems, which may be involved not only in vascular regulation but in the regulation of growth, repair and inflammation. The current concepts of the pathways within the RAS is depicted in Figure 1, including the recent discovery of angiotensin-converting enzyme (ACE2), which has uncovered an arm of the RAS that counterbalances the effects of angiotensin II [8]. A number of conditions causing HT do so, at least in part, via alterations in the RAS [7].

The most common category of secondary HT in childhood is renal parenchymal disease, which includes a wide spectrum of conditions that include activation of the RAS. For example, while many structural anomalies are rarely associated with HT, vesicoureteral reflux (VUR), obstructive uropathy as in ureteropelvic junction obstruction (UPJO) may result in increased intra-renal interstitial pressure, eventual interstitial fibrosis and scarring. One result is activation of the intrarenal RAS.

Patients with a variety of renal cystic diseases, such as autosomal recessive and autosomal dominant polycystic kidney disease (PKD) commonly have HT, which is often difficult to treat. In PKD, not only the RAS, but also sympathetic nervous activity is increased.

Systemic conditions associated with HT such as a variety of glomerulonephritides and vasculitides are associated with HT. Acute post-infectious glomerulonephritis is typically associated with HT, as are chronic glomerular diseases such as IgA nephropathy, membrano-proliferative glomerulonephritis and primary membranous nephropathy. In these conditions, there is often evidence of RAS activation but also of endothelial inflammation, sympathetic activation and aberrant sodium handling.

The HT associated with chronic renal insufficiency appears to be multifactorial. With progressive nephron loss, salt and water handling is aberrant, and the incidence of peripheral vascular disease may be increased from complications of accompanying metabolic changes such as dyslipidemia. Moreover, increased proteinuria may lead to further glomerular injury and renal parenchymal fibrosis, exasperating the RAS-induced HT.

Patients with solid organ transplants, particularly

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**FIGURE 1.** Angiotensin-converting enzyme 2: Implications for blood pressure and kidney disease

*From Ingelfinger JR. Angiotensin-converting enzyme 2: implications for blood pressure and kidney disease. Curr Opin Nephrol Hypertens 2009; 18: 79-84 (with permission).*
renal, often develop HT. The mechanisms of transplant-associated HT are complex and related to a number of issues such as original disease, medications, and stability of the transplant. There may be alterations in salt and water transport, and increased RAS, and sympathetic nervous system activities. The immunosuppressive regimens in transplantation often result in iatrogenic HT from glucocorticoids, calcineurin-inhibitors and other agents described below. The treatment of malignancies and other conditions can result in acute kidney injury or secondary mineralocorticoid stimulation with consequent HT [9].

RENOVASCULAR DISEASE

Renal vascular disease with or without systemic vascular disease is commonly associated with HT. Diseases such as fibromuscular dysplasia (FMD), moyamoya syndrome and collagen vascular diseases, such as Ehler Danlos and Marfan’s syndromes, can all lead to renal blood flow compromise and hence increased RAS activity [10]. Certain cardiovascular anomalies such as coarctation of the aorta also result in renal hypoperfusion with consequent renin release and HT.

Prematurity and low birth weight are both identified with adult HT. A number of lines of evidence lead to the concept that this effect is mediated by relatively low nephron mass and consequent glomerular hypertrophy, fibrosis and renin-mediated HT. However, in infants who require neonatal intensive care, there are additional causes of early HT. For example, invasive neonatal ICU monitoring with umbilical vascular catheterization occasionally lead to renal arterial damage or renal vein thrombosis and consequent renal ischemia and increased renin levels [11]. Further, genetic variations in the RAS have recently been identified and appear to influence cardiovascular health [12].

IATROGENIC HYPERTENSION

A variety of over-the-counter or prescription medications may lead to HT. The mechanisms by which these medications lead to HT varies, depending on the substance. Over-the-counter cold and cough medications may be abused by adolescent teenagers for their psychogenic effects, but often lead to cardiovascular complications including marked HT and even sudden death [13]. Some medications ultimately cause interstitial injury, for example, non-steroidal anti-inflammatory drugs [NSAIDS]. The mechanisms are complex, but some ascribe the hypertensive effects as renin-mediated [14].

Glucocorticoids, often used for treatment of inflammatory renal disease, may worsen existing HT or may induce it. A major mechanism is via an increase in renal tubular sodium uptake with consequent expanded intravascular volume. In addition to glucocorticoids, several immunosuppressive medications used in organ transplantation, cancer chemotherapy, rheumatologic disease, among others cause HT by direct renal tubular and consequent glomerular damage, leading to nephron loss.

Certain foods contain substances such as the glycyrrhizic acid in licorice which activates mineralocorticoid receptors, leading to HT [15].

OBESITY-RELATED HYPERTENSION

The pathogenesis of HT in obesity is multi-factorial and incompletely understood; it may include activation of the leptin-adiponectin pathway with consequent insulin resistance, increased sodium reabsorption and increased RAS activity, all of which can lead to increased cardiac output, endothelial dysfunction and, ultimately, persistent HT [16]. The type of diet in both normal and overweight persons is also important in setting BP level via influences in fluid retention and vascular. Diets high in sodium and low in potassium are associated with higher BP via their effects on fluid retention and vascular tone. Consequently, a diet that is low in sodium and rich in potassium sources such as fruits and vegetables, may have important therapeutic consequences. Sodium sensitivity is more common in certain ethnicities and has a higher prevalence among blacks [17-18].

ENDOCRINE-MEDIATED HYPERTENSION

Hypertension of endocrine etiology is relatively rare, with pathophysiology related to the involved endocrine system. There are multiple types of adrenal-mediated HT seen in children, some of which were originally thought to be primary.

Several forms of congenital adrenal hyperplasia result in increased mineralocorticoid effect, with sodium and fluid retention [19]. In addition, frank hyperaldosteronism may occur with aldosterone-secreting masses. Further, a number of monogenic disorders (discussed elsewhere in this issue of the LMJ), are associated with HT and/or often identifiable because of low renin HT.

Increased secretion of cortisol by the adrenal may occur via tumor and lead to Cushing’s syndrome. Even more commonly, however, exogenous steroids may result in hypercortisolism. Cushing’s disease, leading to HT as a consequence of increased secretion of ACTH may also lead to hypercortisolism.

The adrenal medulla [and other sources of chromaffin cells] may be involved in catecholamine-secreting tumors. While rare, catecholamine-mediated HT, such as pheochromocytomas, is important to identify [2].

Other endocrine etiological factors include congenital and inflammatory thyroid disease such as hyperthyroidism and more recently identified, hypothyroidism may underlie secondary HT in children. In addition, increased activity of the parathyroid glands has been associated with HT, considered to be mediated through vascular and myocardial calcification and increased stiffness with time [20].
NEUROLOGICAL CAUSES OF HYPERTENSION

This category of causes for hypertension includes the central and peripheral nervous systems and is incompletely understood. Several small molecule neurotransmitters, including amino acids aspartate and glutamate, biogenic amines such as noradrenaline, dopamine and serotonin, and peptides such as vasopressin and angiotensin II are involved in the regulation of cardiac output and vascular tone. The reader is referred to a recent review [21].

MISCELLANEOUS CAUSES OF HYPERTENSION

Stress, is a multi-component factor leading to HT through the hypothalamic-pituitary-adrenal and peripheral nervous system, obesity and its complications described above [22].

SUMMARY

Once HT in childhood is accurately confirmed by several BP determinations, it is important for the clinician to seek a primary cause for the BP elevation, particularly in young children. Seeking the cause via a pathophysiological approach can guide the clinician towards a more specific and rational choice of therapy. Older children and, increasingly, younger children, even prepubertal, are more likely to have primary than secondary hypertension; thus, clinicians should focus on family history and environmental factors that can help identify the diagnosis and guide their therapy. Obesity, an increasing problem worldwide, has become an increasingly important cause of HT in children. Indeed, if the HT epidemic continues, obesity-associated HT may supersede other types of HT, with devastating adult onset consequences such as coronary artery disease. Finally, evolving pharmacogenetic and pharmaco-metabolic technologies by addressing the specific molecular targets behind each category of HT may in the not-too-distant future guide clinicians in tailoring an even more individualized or marker-specific therapy even within the same class of HT [23-24]. Such an approach requires the collaboration between physicians, together with medical scientists, epidemiologists, and even policymakers in order to deliver a comprehensive solution to the increasingly pervasive problem of HT, whether in the adult or pediatric population [25]. Indeed, childhood HT may be considered as the tip of an iceberg — an important finding that should be investigated, as its implications extend far beyond infancy, childhood and adolescence.

REFERENCES


