Monogenic Hypertension in Children: A Review With Emphasis on Genetics

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Hypertension (HT) is a public health problem in children particularly related to the epidemic of overweight and obesity. Monogenic forms of HT are important in the differential diagnosis in children presenting with severe or refractory HT, who have a family history of early-onset HT, unusual physical examination findings, and/or characteristic hormonal and biochemical abnormalities. Most genetic defects in these disorders ultimately result in increased sodium transport in the distal nephron resulting in volume expansion and HT. Genetic testing, which is increasingly available, has diagnostic, therapeutic, and predictive implications for families affected by these rare conditions.

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INTRODUCTION

Hypertension (HT) is defined as average systolic blood pressure (BP) and/or diastolic BP that is ≥95th percentile for gender, age, and height on at least 3 occasions. The prevalence of pediatric HT is about 3% in children and adolescents.[1-3] Although HT is less common in children than in adults, there is increasing concern about it because of the association of elevated BP with the epidemic of overweight and obesity.[1,4]

It has been hypothesized that cardiovascular functions are determined in childhood and track into adulthood.[5] Although death and cardiovascular disability are not usually seen in hypertensive children, intermediate markers of target organ damage such as left ventricular hypertrophy and microalbuminuria are more commonly found.[6,7] Early identification and appropriate treatment is crucial to prevent long-term consequences of uncontrolled HT. This requires workup to find the mechanism of HT in each patient, particularly those with unusual clinical features such as those described in this manuscript. Nondirected therapy can be ineffective and comes with side effects. Additionally, there is a paucity of data on the long-term effects of antihypertensive drugs on growth and development. Therefore, securing the accurate diagnosis before initiating a specific pharmacologic therapy is critical. The purpose of this paper is to review clinical information regarding monogenic HT in children and to discuss the utility of genetic testing in optimizing management of these rare but important forms of HT.

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WHEN TO SUSPECT A MONOGENIC HYPERTENSION

Before labeling an HT as idiopathic, a very thorough search for secondary causes should be undertaken particularly in the pediatric population. Monogenic HT is an important consideration for patients presenting with one or more features described below.

1. Early-onset HT
2. Severe or refractory HT
3. Family history of childhood HT (in autosomal dominant [AD]/autosomal recessive [AR] disorders) and history of consanguinity (in AR disorders).
4. Clues from physical examination which may indicate an underlying genetic syndrome (Table 1).
5. Specific biochemical and hormonal abnormalities.

ROLE OF GENES IN HYPERTENSION

Genes make an important contribution to HT in 2 different ways:

1. Polygenic/primary HT—These are caused by combined action of many common genetic variants and environmental and other risk factors. These genetic variants are individually associated with small effect size.
2. Monogenic (Mendelian) HT/secondary HT—This results from a pathogenic variant (mutation) in a single gene even in the absence of environmental or other risk factors. These include 2 category of disorders:
   a) Diseases which cause HT directly by affecting the kidney (eg, glucocorticoid-remediable aldosteronism) or rarely the blood vessels (eg, *PDE3A*-related HT and brachydactyly syndrome). HT is the predominant and usually the only manifestation of these disorders. These are summarized in Table 2 and discussed in detail below.
   b) Diseases which cause HT indirectly by other mechanisms (eg, Neurofibromatosis, Tuberous Sclerosis). HT is not a predominant manifestation of these disorders.

The impact of monogenic HT at the population level is small because these conditions are rare. The identification of monogenic HT genes has been useful in improving the understanding of pathways involved in BP control.

Genetic testing in patients with secondary HT can facilitate timely diagnosis and eliminate the need for complicated evaluations like dexamethasone suppression test, adrenal imaging, and adrenal-vein sampling. It also permits targeted monotherapy based on the underlying defect in an effort to maximize benefit and minimize drug side effects. Additionally, once the genetic diagnosis is established, additional at risk family members can be tested for the same genetic variant that can increase their chance of developing that disease.

PATHOPHYSIOLOGY

The common defect in almost all the forms of monogenic HT syndromes is the dysregulation of sodium (Na^+) reabsorption at the level of the distal convoluted tubule (DCT) cell and the principal cells of the collecting duct (CD). Na^+ is transported from the lumen to the epithelial cell by thiazide-sensitive sodium chloride cotransporter (NCC) in the DCT and amiloride-sensitive epithelial Na channel (ENaC) in the CD. The expression and transport of these Na^+ channels is regulated by kinase activity such as WNK1 and WNK4 and by mineralocorticoid activity through the mineralocorticoid receptor (MR) on the epithelial cells. The affinity of MR in the kidney is higher for cortisol than for mineralocorticoids such as aldosterone or deoxycorticosterone (DOC). The activity of 11β-hydroxysteroid dehydrogenase (HSD) type 2 converts cortisol to its inactive metabolite cortisone, protecting the mineralocorticoid effect of cortisol in the kidney. Independent of the genetic defect, the final effect in all (but one) forms of monogenic HT is increased Na^+ reabsorption in the kidney causing volume expansion and HT with a suppressed plasma renin activity.[8]

CLINICAL SUMMARY

- Hypertension (HT) is a common clinical feature of many genetic disorders and is the predominant feature in monogenic hypertensive disorders.
- Monogenic HT is an increasing recognized cause of HT in children and young adults.
- Genetics of monogenic forms of HT is an expanding field that provides insight into the pathophysiology of HT, helps to detect risk for disease, guide strategies for maintaining health, offer more accurate diagnosis, and guide treatment choices.

GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM (FAMILIAL HYPERALDOSTERONISM TYPE I)

Glucocorticoid-remediable aldosteronism (GRA; MIM# 103900) is a rare AD disorder caused by unequal crossing over between 2 adjacent genes, *CYP11B1* and *CYP11B2* (code for 11β-hydroxylase and aldosterone synthase, respectively), that are located on chromosome 8q. The chimeric gene has *CYP11B1*-specific adrenocorticotropic hormone (ACTH) responsive promoter and *CYP11B2*-specific aldosterone synthase coding region and encodes a hybrid protein consisting of the amino-terminal portion (exons 1-4) of CYP11B1 and the carboxyl-terminal part (exons 5-9) of CYP11B2. This results in ectopic ACTH-stimulated increased aldosterone production in the zona fasciculate (ZF), independent of renin.[9] The high levels of mineralocorticoids activate the MR and upregulate Na reabsorption and potassium (K) secretion.

Aglony and colleagues reported chimeric *CYP11B1/CYP11B2* prevalence of 3.08% (4 of 130) in their pediatric hypertensive population.[10] Most individuals have severe HT usually before the age of 20 years.[11] Intrafamily variability has been reported with GRA.[12] Patients are at risk for cerebral aneurysms and strokes at a young age (<40 years); therefore, magnetic resonance (MRI/MRA) screening is advised for patients with genetically proven GRA.[13] Plasma renin is low, and yet, plasma aldosterone concentration may be normal. Mild hypokalemia and metabolic alkalosis can be observed. Gene sequencing can provide molecular confirmation for GRA.

Exogenous administration of physiologic low doses of a glucocorticoid is the first-line therapy. Intermediate-acting glucocorticoid (eg, prednisone) administered at bedtime to suppress the early morning surge in ACTH controls the overproduction of aldosterone, ultimately resulting in lower BP.[14] The selection of the glucocorticoid depends upon the growth status and compliance of the patient, with preference of hydrocortisone for growing children and dexamethasone for adults. An alternative approach is treatment with MR antagonists (spironolactone or eplerenone) which avoid the potential disruption of the hypothalamic-pituitary-adrenal axis and risk of iatrogenic side effects. In children, eplerenone is preferable, to avoid the side effects of glucocorticoids (retarded growth) or spironolactone (antiandrogen effects).[15] The therapeutic goal should be normotension and not normalization of biochemical markers such as urinary 18-oxosteroid or serum aldosterone levels. These remain elevated in the majority, even among those whose BP normalizes. Titrating therapy to normalize laboratory values could unnecessarily increase the risk of Cushingoid side effects.[16]

SYNDROME OF APPARENT MINERALOCORTICOID EXCESS (CORTISOL 11β-KETOREDUCTASE DEFICIENCY)

Apparent mineralocorticoid excess (MIM # 218030) is a rare AR disorder due to pathogenic variants in the *HSD11B2* gene (located on chromosome 16q) that result in the expression of HSD with a completely impaired enzymatic activity.[17] HSD type 2 is the kidney isoform of 11β-HSD and normally converts active cortisol to inactive cortisone at the sites of aldosterone action. This conversion is impaired in apparent mineralocorticoid excess. Due to the higher cortisol affinity for the MR, the persistence of cortisol leads to a marked elevation in net mineralocorticoid activity. *HSD11B2* gene

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