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## **Secondary Hypertension in the Pediatric Population**

Ashley M Gefen

### **Diagnosis of Hypertension**

In order to confirm hypertension in the pediatric population, it has been suggested that one should check blood pressures using auscultation rather than electronic measurements, as pediatric standard normotensive blood pressures are measured via auscultation [1].

Prehypertension is defined as blood pressures between the 90<sup>th</sup> percentile and less than the 95<sup>th</sup> percentile, or blood pressures >120/80 mmHg, even if less than the 90<sup>th</sup> percentile for age [2]. Stage 1 hypertension is defined as blood pressures between the 95<sup>th</sup> percentile and 5 mmHg above the 99<sup>th</sup> percentile [2]. Stage 2 hypertension is defined as blood pressures greater than 5 mmHg above the 99<sup>th</sup> percentile [2]. The diagnosis of hypertension, can be made if blood pressure measurements are in the hypertensive range for sex, age, and height on three separate occasions [2]. If the patient is asymptomatic but found to be hypertensive, blood pressures can be checked again at least 1 week later to confirm the presence of hypertension [1]. If the patient is hypertensive and symptomatic, immediate evaluation and treatment is required [1].

Ambulatory blood pressure monitoring (ABPM) can be an effective method of confirming hypertension and differentiating between white coat hypertension, masked hypertension, and true hypertension [3]. Using ABPM, higher nocturnal systolic blood pressure (SBP) load and 24 hour diastolic blood pressure (DBP) load have been reported to be specific for secondary hypertension rather than primary hypertension [3].

Blood pressures should be measured in all children above 3 years of age as well as in younger children with certain predisposing factors such as: prematurity, low birth weight, umbilical artery catheterization; congenital heart, renal, or urologic malformations; history of urinary tract infections (UTIs), hematuria, proteinuria; solid organ or bone marrow transplant; malignancy; medications associated with hypertension; conditions associated with hypertension; and raised intracranial pressure (ICP) [3].

### **Initial Evaluation of Patients with Hypertension**

Once hypertension is confirmed, a detailed history and physical, as well as targeted labs and imaging, should be performed to determine the etiology of hypertension. The list of secondary causes of hypertension is extensive, and a detailed evaluation is not warranted or effective in everyone with elevated blood pressures [3]. A baseline evaluation is the most first step.

Important information to obtain from the history includes questions to elicit a possible causal etiology (either primary or secondary), as well as the degree of end organ damage present [1]:

- Symptoms that would suggest endocrine pathology such as heat intolerance, flushing, diaphoresis, weight loss or gain
- History of prematurity / low birth weight / umbilical artery catheterization
- History of UTIs
- Symptoms suggesting sleep pathology such as obstructive sleep apnea (OSA) (e.g. daytime sleepiness)

- List of medications
- Family history of hypertension or end stage renal disease (ESRD)
- Diet including caffeine and salt intake
- Use of illicit drugs, alcohol, or tobacco
- Level of physical activity
- History suggestive of end organ damage such as headaches, dizziness, epistaxis, visual changes, chest pain, facial palsy [3]

A thorough physical examination can also reveal important clues as to the cause of hypertension (either primary or secondary), as well as the degree of end organ damage present [1]:

- Vitals with four extremity blood pressure, pulse, weight
- Neck exam for thyromegaly
- Findings to suggest a syndromic illness such as webbed neck or elfin facies
- Skin findings such as rashes or lesions
- Cardiovascular evaluation for murmurs, rubs, bruits, edema
- Apical heave can indicate left ventricular hypertrophy (LVH), end organ damage resulting from high blood pressures
- Abdominal exam to palpate for masses
- Fundoscopy to evaluate for retinal abnormalities suggestive of end-organ damage from high blood pressures as 51% of children with hypertension have been found to have retinal abnormalities [3]

A number of laboratory tests are warranted for a baseline evaluation of all patients presenting with hypertension [3]: a basic metabolic panel including potassium, BUN, creatinine;

complete blood count to evaluate for anemia; urinalysis to evaluate for hematuria, proteinuria, or casts; some suggest acquiring an early morning urine protein to creatinine ratio [4].

In terms of initial imaging, renal US with Doppler is crucial in evaluating renal parenchymal disease or renovascular disease [1]. Kidney vascular and parenchymal disease are responsible for most cases of pediatric secondary hypertension. Echocardiogram is important to obtain in order to evaluate left ventricular mass for LVH [4]. Echocardiogram can also be useful to rule out aortic coarctation [4].

If baseline evaluation is normal, primary hypertension is the likely diagnosis, especially in adolescent patients [3]. Obese patients with hypertension are also more likely to have primary hypertension [3]. Clues that a patient has a metabolic syndrome predisposing them to hypertension include poor diet and low level of physical activity on history, as well as obesity and acanthosis nigrans on physical exam [3]. If baseline evaluation is not normal or in younger children with normal baseline evaluation, secondary hypertension should be evaluated [3].

## **Causes of Secondary Hypertension**

### **Renal parenchymal**

Renal parenchymal disease accounts for the majority of secondary hypertension [1]. Renal scarring, often due to reflux nephropathy, accounts for about 79% of all causes of secondary hypertension [3]. Congenital renal malformations affecting the kidney vascular system (e.g. from Turner syndrome) also contribute [3]. Polycystic kidney disease can cause hypertension and typically presents with a family history of kidney disease, abdominal mass, and hepatosplenomegaly [3]. Chronic kidney disease can lead to hypertension and is often

associated with growth failure and pallor from anemia [3]. Wilms tumor, the most common renal malignancy in children, will typically present with an abdominal mass and can lead to hypertension [3].

Systemic vasculitis (e.g. Lupus, PAN, HSP, ANCA) and acute or chronic glomerulonephritis can cause hypertension and often have associated physical exam findings specific to each disease process, as well as abnormalities on urinalysis [1, 3]. For example, lupus can present with malar rash, joint pains, photosensitivity, anemia, and urinalysis with blood and/or protein. HSP can present with abdominal pain, palpable purpura, and urinalysis with blood and/or protein. Post-streptococcal glomerulonephritis typically present after streptococcal infection with tea-colored urine and urinalysis with blood, protein, and red blood cell casts.

If your baseline evaluation has led you suspect renal parenchymal disease as the cause of secondary hypertension in your patient, further renal imaging or blood tests may be warranted to confirm diagnosis [1].

## **Endocrine**

Endocrine disease accounts for approximately 10% of secondary hypertension in children [1]. Causes include hyperaldosteronism, hypercalcemia, pregnancy, pheochromocytoma, neuroblastoma, hyperthyroidism, Cushing's syndrome, and congenital adrenal hyperplasia (CAH) [3].

Pheochromocytoma can be sporadic or can be associated with genetic disorders such as Multiple Endocrine Neoplasia type 2 (MEN 2), Neurofibromatosis type 1 (NF1), von Hippel-Lindau (VHL), and familial paraganglioma [3]. Genetic associations will be discussed later. With pheochromocytoma, patients can have a history of headache, abdominal pain, nausea, and vomiting [3]. On physical exam they can exhibit tachycardia, pallor, flushing, diaphoresis, orthostatic hypotension, and abdominal mass [3]. Neuroblastomas can also present with

tachycardia and abdominal mass [3]. Pheochromocytomas can be screened for by measuring plasma free metanephrines or 24-hour urine metanephrines. The diagnosis can be confirmed via CT, MRI, or the nuclear medical scan using the metaiodobenzylguanidine tracer (MIBG scan) [3].

Hyperthyroidism causes to increased cardiac output and decreased systemic vascular resistance, resulting in isolated systolic hypertension with a widened pulse pressure [3]. Patients can present with weight loss, heat intolerance, tachycardia, diaphoresis, exophthalmos, tremor, hyperactive reflexes, and thyromegaly [3]. The diagnosis can be confirmed with thyroid function tests [3].

Cushing's syndrome can present with truncal obesity, moon facies, abdominal striae, acne, and hirsutism [3]. It can be screened for with morning plasma cortisol and should be managed by a pediatric endocrinologist [3].

Two subtypes of CAH can lead to hypertension, but will be discussed later along with other forms of monogenic hypertension.

## **Renovascular**

Renovascular disease also accounts for approximately 10% of cases of secondary hypertension [1]. Examples include midaortic syndrome [1], renal vein thrombosis, arteritis (Takayasu's, Kawasaki, Moyamoya), vascular compression by tumor, retroperitoneal fibrosis, and genetic syndromes such as Williams syndrome, Turner syndrome, and NF1 [3]. Initial renal ultrasound with Doppler may help make a diagnosis, but further evaluation can be performed with different imaging such as a CTA or MRA [1].

## **Cardiovascular**

Cardiovascular causes of hypertension include coarctation of the aorta and syndromes with aortic hypoplasia (e.g. Williams syndrome, Turner syndrome) [1, 3]. Aortic coarctation is a

common cause of hypertension in first year of life [3]. It often presents with delayed and weak femoral pulses, normal or low blood pressure in the legs, and a heart murmur most prominent in the interscapular area [3]. Coarctation can be confirmed with echocardiogram [3].

### **Pulmonary**

OSA is a pulmonary cause of hypertension that often presents with nighttime awakenings, witnessed apnea during sleep, snoring, and daytime somnolence [1]. It is typically associated with increased nighttime diastolic blood pressures [3]. If clinical suspicion is high, OSA can be evaluated for with polysomnography [1].

### **Neurologic**

Various neurologic problems can cause high blood pressure including increased intracranial pressure (ICP), vasomotor center abnormalities, sympathetic nervous system abnormalities, seizures, Riley-Day syndrome, nerve traction, and cyclic vomiting syndrome [1, 3]. Increased ICP is an important cause of hypertension that should not be missed. It can present with headache, nausea, vomiting, and papilledema on funduscopic exam [1].

### **Iatrogenic**

Hypertension can also be induced iatrogenically. It is important to consider the use of IV fluids, steroids, calcineurin inhibitors, oral contraceptives, ADHD medications, anesthetics, EPO, and illicit drugs when determining the cause of hypertension in a patient [3].

### **Monogenic Hypertension with Low Renin**

There are a number of genetic disorders associated with hypertension in the pediatric population. Although they are rare, they are common enough to warrant evaluation. One should

have an increased suspicion for monogenic forms of hypertension with low renin with the presence of abnormal potassium levels (low or high) and alkalosis (or acidosis) [4]. Family history with early onset hypertension may indicate autosomal dominant inheritance [4]. Consanguinity may indicate autosomal recessive inheritance [4].

There are three distinct mechanisms that lead to final result of increased sodium reabsorption, volume expansion, and resulting low plasma renin [4]:

1. Excessive aldosterone synthesis (e.g. Glucocorticoid remediable aldosteronism)
2. Gain-of-function mutations that lead to increase sodium and chloride absorption (e.g. Liddle's, Gordons)
3. Deficiencies of enzymes that regulate adrenal steroid hormone synthesis and deactivation (e.g. CAH, apparent mineralocorticoid excess)

### **High to normal Aldosterone**

#### *Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type 1)*

Results from unequal crossover between the 11-beta-hydroxylase coding gene and the aldosterone synthase gene, resulting in ACTH-stimulated aldosterone production [4]. It is inherited in an autosomal dominant fashion and is typically absent in African Americans [4]. Diagnosis can be made by checking urine steroid hormones [4]. This should show a high 18-oxotetrahydrocortisol and 18-hydroxycortisol to tetrahydroaldosterone ratio [4]. Afterward, genetic testing can be performed for the chimeric gene [4]. This condition is treated with steroids to suppress ACTH production and therefore aldosterone synthesis. Amiloride or triamterene can also be added to block sodium reabsorption in the principal cell of the collecting duct [4]. These patients should be screen for cerebral aneurysms starting at puberty as they are at increased risk [4].

### *Type 2 pseudohypoaldosteronism / Gordon's*

Results from mutations in WNK1 and WNK4, causing increased uptake by the thiazide-sensitive sodium chloride cotransporters in the distal convoluted tubule [4]. This increase in uptake of chloride causes decreased potassium and hydrogen ion secretion into the urine [1]. This is the only low-renin monogenic form of hypertension that often results in hyperkalemia with a hyperchloremic metabolic acidosis [1, 3, 4]. Hypercalcemia also often results. Inheritance is autosomal dominant [4]. Treatment is with a low-dose thiazide diuretic [4].

### **Low Aldosterone**

#### *Apparent mineralocorticoid excess*

Results from inactivation of the 11-beta-hydroxysteroid dehydrogenase (HSD) type 2 enzyme, resulting in decreased cortisol breakdown and stimulation of aldosterone receptors [1, 4]. Patients typically present with hypokalemia and a resulting renal concentrating defect, alkalosis, and hypercalciuria with nephrocalcinosis [3, 4]. Urinary steroid hormone profiling shows increased free cortisol to free cortisone ratio [4]. This disease can easily be mistaken with liquorice abuse as it inhibits the 11-beta-HSD type 2 enzyme [4]. Apparent mineralocorticoid excess is a rare autosomal recessive condition [4]. Confirmatory genetic testing is available [4]. Treatment involves salt restriction and medications such as spironolactone or eplerenone, and amiloride [1, 4]. Thiazide diuretics may decrease associated hypercalcemia [4].

#### *Congenital Adrenal Hyperplasia*

Two subtypes of CAH can lead to hypertension, both are inherited in an autosomal recessive pattern [3]. 11-beta-hydroxylase deficiency causes increased sex hormone production as well as increased cortisol precursors that lead to increased

mineralocorticoid production [3]. Females present with ambiguous genitalia [3]. Males present with precocious puberty [4]. Labs tend to show hypokalemia and alkalosis [3]. Urine steroid hormone profile should be checked [4]. 11-beta-hydroxylase deficiency is treated with steroids and spironolactone or eplerenone [1, 4].

17-alpha-hydroxylase deficiency leads to increased cortisol and aldosterone production with a decrease in sex hormone production [3]. Females present with absent secondary sexual characteristics and primary amenorrhea [3]. Males present with ambiguous genitalia [4]. Labs tend to show hypokalemia and alkalosis [3]. Urine steroid hormone profile should be checked [4]. 17-alpha-hydroxylase deficiency is treated with steroids, sex hormones, and spironolactone or eplerenone [4].

### *Liddle syndrome*

Results from increased epithelial sodium channel (ENaC) activation and therefore sodium reabsorption in the distal tubule [1, 4]. This results in hypokalemia, alkalosis, and sometimes hypercalciuria [3, 4]. It is inherited in an autosomal dominant fashion [4]. Treatment involves a low sodium diet and amiloride or triamterene [1]. Aldosterone receptor antagonists such as spironolactone have no effect as there is constitutive expression of ENaC independent of the mineralocorticoid receptor (MR) [4].

## **Other Genetic Causes of Hypertension**

### *Type 1 pseudohypoaldosteronism*

Two subtypes of can lead to hypertension, one is autosomal recessive and one is autosomal dominant [1]. The recessive form results from a loss of function of ENaC, leading to water and salt wasting and subsequent hyperaldosteronism [4]. The dominant form results from a loss of function mutation of aldosterone receptors, leading to aldosterone resistance [1].

Patients typically have increased renin and aldosterone [4]. Treatment involves salt supplementation [1].

### *Familial hyperaldosteronism type 2*

Results from increased aldosterone production by the adrenal glands [5]. Patients present with hypokalemia, alkalosis, and low renin [5]. The disease is inherited in an autosomal dominant fashion, although the gene is currently unknown [5].

### *Pheochromocytoma associated genetic disorders*

These include MEN 2, VHL, NF1, and familial paraganglioma [3]. Approximately 30% of pheochromocytomas are thought to be caused by germline mutations [6]. MEN 2 is an autosomal dominant condition due to a RET proto-oncogene mutation [6]. It can present with medullary carcinoma and hyperparathyroidism in MEN 2A, or mucosal neuromas and Marfanoid habitus in MEN 2B. VHL results from a mutation in tumor suppressor gene VHL. It can present with retinal hamartomas [3, 6]. NF1 can present with café au lait spots, axillary freckling, cutaneous neurofibromas, and Lisch's nodules (iris hamartoma) [3, 4]. NF1 is associated with pheochromocytomas and renovascular abnormalities, sometimes due to vascular compression from plexiform neuromas [3].

### *Turner Syndrome*

Turner syndrome can present with webbed neck, widely spaced nipples, short fourth metacarpal, short stature, and swollen hands and feet as a neonate [3, 4]. There is an increased risk of congenital renal anomalies, aortic hypoplasia, renovascular disease, and aortic coarctation [3].

### *Williams syndrome*

Williams syndrome can present with elfin facies, short stature, and cardiac murmur [3, 4]. It is associated with renovascular abnormalities, often due to a midaortic syndrome [3].

### *Tuberous sclerosis*

Tuberous sclerosis can present with facial angiofibroma, hypomelanotic macules, and shagreen patches [4]. There is an increased risk of renal compression [4].

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