



## Pediatric Endocrine Hypertension Related to the Adrenal Glands

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Endocrine causes of pediatric hypertension are relatively rare but important because of their distinct treatment options. Adrenal diseases accompanied by an excess of mineralocorticoids, glucocorticoids, and catecholamines are major causes of endocrine hypertension. Typical causes of mineralocorticoid-related hypertension include primary aldosteronism, congenital adrenal hyperplasia (11 $\beta$ - and 17 $\alpha$ -hydroxylase deficiencies), and apparent mineralocorticoid excess. Cushing syndrome and pheochromocytoma/paraganglioma are the primary causes of glucocorticoid- and catecholamine-related hypertension, respectively. This review provides an overview of the diagnostic evaluations, including hormonal assays and imaging studies, used to identify the underlying causes of pediatric endocrine hypertension, focusing on adrenal disorders. It presents details regarding the major adrenal disorders and recommended therapeutic approaches, emphasizing the importance of early detection and disease-specific management to prevent cardiovascular and metabolic complications in affected children.

## Introduction

Pediatric hypertension is defined as systolic and/or diastolic blood pressure (BP) at or above the 95th percentile based on the normative distribution by age, sex, and height (or  $\geq 130/80$  mmHg for children aged  $\geq 13$  years) [1]. The recognition of hypertension in childhood is on the rise, with a global prevalence of approximately 4.0% [2]. Among pediatric hypertension cases, 50% are due to secondary causes, with endocrine hypertension comprising up to 6% [3]. Aside from obesity-related hypertension, the primary endocrine disorders that cause hypertension in children are adrenal diseases characterized by an overproduction of catecholamines, glucocorticoids, and mineralocorticoids [4]. Non-adrenal endocrine disorders such as excess growth hormone, thyroid dysfunction, and hyperparathyroidism also lead to hypertension [4]. When evaluating a patient with suspected endocrine-related hypertension, clinicians should obtain a detailed medical history, a review of systems including disease-specific symptoms and signs, and a family history of endocrine hypertension. Identifying an endocrine cause in children with hypertension not only opens the door to potential surgical cures or targeted pharmacological treatments but also aids in the prevention of metabolic and cardiovascular sequelae [5]. This review provides an overview of the biochemical and clinical features of childhood endocrine hypertension, with a particular emphasis on adrenal disorders and a discussion of their treatment options.

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## Biosynthesis and Action of Adrenal Hormones

The adrenal cortex produces three primary classes of steroid hormones that are essential for regulating a variety of physiological processes: mineralocorticoids from the zona glomerulosa, glucocorticoids from the zona fasciculata, and adrenal androgens from the zona reticularis [6]. Mineralocorticoids, with aldosterone being the most prominent, function by binding to the mineralocorticoid receptor (MR) and carry out a crucial role in BP regulation by modulating renal sodium reabsorption, as well as the release of hydrogen and potassium ions in the distal nephrons [7]. Glucocorticoids, predominantly cortisol, interact with the glucocorticoid receptor and are involved in regulating a wide range of bodily functions, including the mobilization of carbohydrates [8]. The adrenal medulla synthesizes and secretes catecholamines, including dopamine, norepinephrine, and epinephrine [9]. These catecholamines are released in response to stress, leading to an increase in BP, heart rate, and cardiac output, as well as alterations in smooth muscle tone [10]. Table 1 lists the major adrenal disorders that can lead to pediatric hypertension.

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## Mineralocorticoid-Related Hypertension

### 1. Primary aldosteronism

Primary aldosteronism (PA), the most prevalent type of secondary hypertension, accounts for approximately 10% of cases of pediatric hypertension [11]. In this condition, the adrenal glands autonomously produce aldosterone, resulting in low plasma renin activity, hypokalemic acidosis, polyuria, and hypertension. PA manifests with a wide range of severity, from mild to severe, and may initially present as elevated BP without concurrent hypokalemia or low renin activity [12].

The primary causes of PA are unilateral aldosterone-producing adenomas (also known as Conn syndrome, accounting for 30%–40% of cases), bilateral idiopathic hyperaldosteronism (comprising 60%–70% of cases), and less common forms (e.g., familial hyperaldosteronism [FH], representing 1%–5% of cases, and primary nodular adrenal hyperplasia). It is crucial to distinguish PA from physiological hyperreninemic hyperaldosteronism, which arises in response to sodium loss, potassium retention, or reduced blood volume. The diagnosis of PA is based on elevated plasma aldosterone levels and low plasma renin concentrations, resulting in an increased aldosterone-to-renin ratio (ARR). PA can be definitively diagnosed or excluded without the need for dynamic confirmatory testing in patients who present with an ARR greater than 27 ng/dL per ng/mL/h and a plasma aldosterone concentration exceeding 20 ng/dL, or in those with a normal ARR and a plasma aldosterone concentration below 9 ng/dL on two separate occasions [13]. For cases in the gray zone, dynamic aldosterone suppression tests are recommended, which may involve intravenous or oral saline loading, the administration of fludrocortisone, or captopril as an angiotensin-converting enzyme inhibitor [13]. PA is classified as either unilateral or bilateral using adrenal imaging and adrenal vein sampling [14]. The treatment of PA involves unilateral adrenalectomy in cases of lateralized aldosterone-producing adenoma or adrenal hyperplasia, and MR antagonists are used to treat bilateral PA [14].

Four subtypes of FH with autosomal dominant inheritance have been described. FH type I (OMIM 103900), caused by the chimeric *CYP11B1/CYP11B2* gene, can be treated with glucocorticoids [15]. FH type II (OMIM 605635) is associated with germline variants of *CLCN2* and does not respond to glucocorticoid administration [16]. FH type III (OMIM 613677) has been linked to germline variants of *KCNJ5* and is characterized by severe PA and hypokalemia due to

**Table 1.** Adrenal disorders causing pediatric hypertension

Disease	Gene	Inheritance	Clinical findings	Diagnostic tools
Mineralocorticoid-related hypertension				
Primary aldosteronism	–	–	Polyuria, myopathy cardiac dysrhythmias (in severe hypokalemia)	Increased aldosterone, suppressed PRA Increased aldosterone/renin ratio Low potassium
FH type I (OMIM 103900)	Chimeric <i>CYP11B1/CYP11B</i>	AD	Early and severe hyperaldosteronism relieved by treatment with glucocorticoids; variable presentation within the same family but associated with high morbidity and mortality at an early age	Germline mutation testing
FH type II (OMIM 605635)	<i>CLCN2</i>	AD	Early-onset hyperaldosteronism; variable phenotypic presentation, incomplete penetrance	
FH type III (OMIM 613677)	<i>KCNJ5</i>	AD	Severe early-onset resistant arterial hypertension and hypokalemia with massive bilateral adrenal hyperplasia; high levels of 18-oxocortisol and 18-hydroxycortisol; mild forms are also described	
FH type IV (OMIM 617027)	<i>CACNA1H</i>	AD	Early-onset hyperaldosteronism; developmental delay or attention-deficit disorder in some patients	
11 $\beta$ -Hydroxylase deficiency (OMIM 202010)	<i>CYP11B1</i>	AR	Virilization (female), pseudoprecocious puberty, sometimes prepubertal gynecomastia (male)	Increased 17-hydroxyprogesterone, DOC, 11-deoxycortisol, androstenedione, testosterone, DHEA-S Germline mutation testing
17 $\alpha$ -Hydroxylase deficiency (OMIM 202110)	<i>CYP17A1</i>	AR	DSD (male), sexual infantilism, primary amenorrhea (female)	Low/low normal blood levels of androstenedione, testosterone, DHEA-S, 17-hydroxyprogesterone, aldosterone, cortisol Germline mutation testing
Apparent mineralocorticoid excess/11 $\beta$ -hydroxysteroid dehydrogenase deficiency (OMIM 218030)	<i>HSD11B2</i>	AR	Failure to thrive, delayed puberty, polydipsia, polyuria, muscle weakness, hypertension, nephrocalcinosis	Hypokalemia, metabolic alkalosis Low renin, low aldosterone Normal plasma cortisol levels High urinary cortisol-cortisone ratio
Glucocorticoid-related hypertension				
Cushing syndrome	–	–	Weight gain, growth failure, fatigue, round face, proximal myopathy, plethora, hirsutism, buffalo hump, central obesity	Elevated 24-hr urinary free cortisol excretion for 3 days Loss of circadian rhythm of serum cortisol 1 mg overnight dexamethasone suppression test
Catecholamine-related hypertension				
Pheochromocytoma and paraganglioma	<i>RET, VHL, NF1, SDHD, SDHC, SDHB, SDHA, SDHAF2</i>	AD	Headache, palpitation, sweating, pallor, paroxysmal blood pressure	Fractionated plasma or 24-hr urine metanephrines

PRA, plasma renin activity; FH, familial hyperaldosteronism; OMIM, Online Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; DOC, deoxycorticosterone; DHEA-S, dehydroepiandrosterone sulfate; DSD, disorder of sexual development.

massive bilateral adrenal hyperplasia that cannot be treated with glucocorticoids [17]. FH type IV (OMIM 617027), caused by gain-of-function variants in *CACNA1H*, presents with PA in the first

decade of life but shows incomplete penetrance within affected families (Table 1) [18].

## 2. Congenital adrenal hyperplasia: 11 $\beta$ - and 17 $\alpha$ -hydroxylase deficiencies

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from biochemical defects in steroid biosynthesis, leading to various alterations in mineralocorticoids, glucocorticoids, and adrenal androgens [19]. Hypertension is associated with CAH caused by 11 $\beta$ -hydroxylase deficiency (11OHD) and 17 $\alpha$ -hydroxylase deficiency (17OHD) [20]. 11OHD (OMIM 202010), which results from variants in the *CYP11B1* gene, accounts for roughly 5% of all CAH cases [20]. The enzyme 11 $\beta$ -hydroxylase is responsible for converting 11-deoxycortisol to cortisol and deoxycorticosterone (DOC) to corticosterone. A deficiency in this enzyme causes the overproduction of steroid precursors, such as 11-deoxycortisol and DOC, as well as adrenal androgens, and results in increased secretion of adrenocorticotrophic hormone (ACTH) [20]. The overproduction of DOC leads to hypertension, hypokalemia, and sodium retention, as well as suppressing aldosterone secretion and plasma renin activity to varying degrees [21]. Hypertension may be present in 30%–60% of cases during childhood, and can even be evident at birth. Excess androgens may cause prenatal virilization in females or precocious puberty in both sexes. The diagnosis is confirmed by elevated levels of DOC and 11-deoxycortisol, along with normal or suppressed plasma renin activity (Table 1) [21]. The treatment for 11OHD includes glucocorticoid replacement, using doses similar to the dosage for 21-hydroxylase deficiency, but there is no need for mineralocorticoid replacement [21].

17OHD (OMIM 202110), caused by variants in the *CYP17A1* gene involved in cortisol and androgen biosynthesis, is a highly uncommon type of CAH that is present in approximately 1% of all CAH cases [22]. The enzyme 17 $\alpha$ -hydroxylase converts progesterone to 17-hydroxyprogesterone and pregnenolone to 17-hydroxypregnenolone. Deficient enzymatic activity results in decreased levels of 17-hydroxypregnenolone and 17-hydroxyprogesterone, reduced cortisol synthesis, overproduction of ACTH and elevated levels of DOC [22]. This impaired androgen production leads to the absence of secondary sexual characteristics during puberty in 46,XX individuals, who typically present as teenage girls with sexual infantilism and hypertension [23]. Individuals with a 46,XY karyotype may present with a disorder of sexual development, characterized by absent or incomplete development of the external genitalia (Table 1) [21]. Glucocorticoid replacement therapy is used to suppress hypertension induced by excess mineralocorticoids, and sex steroid replacement is initiated during adolescence, tailored to the individual's sex of rearing [24].

## 3. Apparent mineralocorticoid excess

Apparent mineralocorticoid excess (AME; OMIM 218030) is an autosomal recessive condition that results from pathogenic variants in the *HSD11B2* gene, which encodes the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (HSD11B2). This enzyme is responsible for converting active cortisol into its inactive counterpart, cortisone, in mineralocorticoid-responsive tissues [25]. Children affected by AME typically exhibit severe hypertension, muscle weakness, polyuria, polydipsia, delayed puberty, and failure to thrive, and this condition can lead to early-onset end-organ damage. AME is characterized biologically by hypokalemic alkalosis and low levels of renin and aldosterone. A diagnosis of defective HSD11B2 activity is made by identifying an elevated urinary cortisol-to-cortisone metabolite ratio (Table 1). Treatment options include MR antagonists, such as spironolactone or eplerenone, in combination with potassium-sparing diuretics, hypokalemia correction, and adherence to a low-salt diet. Despite these interventions,

treatment outcomes are not always successful, with a reported cardiovascular mortality rate of 19% among patients with AME [26].

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## Glucocorticoid-Related Hypertension

### 1. Cushing syndrome

Cushing syndrome (CS) is rare in childhood, with two to five new cases per million people annually, and is characterized by excessive production of glucocorticoids [27]. Pediatric CS most commonly arises iatrogenically due to the chronic administration of glucocorticoids. In rarer instances, it is caused by an over-secretion of endogenous cortisol, which can occur through either an ACTH-dependent or an ACTH-independent mechanism [28]. The secretion of excessive amounts of ACTH may be due to pituitary adenomas (known as Cushing disease), and, less commonly, by ectopic ACTH-secreting tumors. ACTH-independent CS takes place when adrenal neoplasms (e.g., carcinomas or adenomas) autonomously secrete cortisol. Another ACTH-independent cause is multinodular adrenal hyperplasia, including massive macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease [29,30]. In children, CS typically presents with weight gain, central obesity, slowed growth, mood changes, altered facial appearance (including plethora, acne, and hirsutism), and muscle weakness. Overweight children who experience a halt in growth should be screened for CS, as weight gain coupled with growth failure are the most consistent and earliest signs [31]. Hypertension is present in about 63% of pediatric cases of CS [32]. When CS is clinically suspected, hypercortisolism is confirmed by a disruption in the normal circadian rhythm of serum cortisol, abnormally high 24-hour urinary free cortisol levels from three consecutive collections, increased levels of late-night salivary cortisol, and/or a lack of serum cortisol suppression following a low-dose dexamethasone suppression test (Table 1) [28,29].

After confirming the diagnosis, additional assessments are needed to determine ACTH dependence and localize the lesion responsible for cortisol secretion. The differential diagnosis should involve measuring plasma ACTH levels, conducting high-dose dexamethasone suppression tests (also known as the Liddle test), and performing a corticotropin-releasing hormone stimulation test [33]. Beyond laboratory tests, imaging studies play a crucial role in accurately diagnosing CS. CT or MRI can be employed to detect tumors of the adrenal cortex or to identify macroscopic or microscopic nodular adrenal hyperplasia. To locate an ectopic ACTH-producing source, CT or MRI scans of the neck, chest, abdomen, and pelvis, along with a labeled octreotide scan and fluorodeoxyglucose (FDG) PET, are utilized [27,29]. The primary treatment objective is the surgical removal of the lesion causing hypercortisolism [34]. While hypertension often improves after surgery, some patients may still need antihypertensive treatment. This can involve blocking the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, as well as targeting glucocorticoid receptors and MRs [35].

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## Catecholamine-Related Hypertension

### 1. Pheochromocytoma and paraganglioma

Pheochromocytoma (PCC) and paraganglioma (PGL) are highly uncommon catecholamine-secreting tumors, accounting for approximately 0.5%–2% of pediatric hypertension cases [36]. PCC originates from the adrenal medulla (more specifically, from chromaffin cells), while

PGLs develop in the autonomic nervous system outside the adrenal glands, arising from both parasympathetic and sympathetic paraganglia external to the cerebrospinal axis [37]. The clinical presentation of PCC and PGL can vary widely, typically involving symptoms and signs of catecholamine excess. The most common symptoms and signs include hypertension, diaphoresis, palpitations, and headache [38]. Occasionally, symptoms such as pain may arise due to the mass effect of the tumor. Some individuals may also be diagnosed incidentally during radiographic evaluations or through family screening for an associated hereditary syndrome [39].

PCC and PGL are diagnosed by measuring the concentrations of catecholamines and their metabolites in samples from the blood and urine. The initial laboratory work-up should include fractionated plasma and/or urine metanephrines (metanephrine and normetanephrine), which have a sensitivity close to 100% (Table 1) [40]. Assessing plasma dopamine or methoxytyramine (a dopamine metabolite) can be helpful for avoiding false-negative results, especially in the rare cases of extra-adrenal succinate dehydrogenase-associated PGLs [41]. Additionally, measurements of chromogranin A, which chromaffin cells store and release together with catecholamines, can serve as an additional diagnostic tool when plasma free metanephrine levels are only mildly elevated [42]. Once biochemical testing confirms catecholamine excess, the tumors can be located through radiographic imaging (typically CT or MRI of the abdomen and pelvis). If abdominopelvic imaging is inconclusive, the next step is to conduct examinations of the neck and chest [43]. Functional imaging can be particularly helpful for confirming extra-adrenal tumors or for evaluating patients for multifocal or metastatic disease, especially in patients who have a noradrenergic phenotype and risk factors for malignancy [44]. Functional imaging options include  $^{123}\text{I}$ - or  $^{131}\text{I}$ -metaiodobenzylguanidine (MIBG), which targets tissues that store catecholamines, and  $^{18}\text{F}$ -FDG PET [45]. A recent study proposed  $^{68}\text{Ga}$ -DOTATATE PET/CT as a first-line imaging modality due to its high affinity for somatostatin receptors, which are prevalent in neuroendocrine tumors like PCC and PGL, and its superior sensitivity compared to  $^{18}\text{F}$ -FDG PET/CT and  $^{123}\text{I}$ -MIBG [46]. Genetic testing to identify common susceptibility genes is advised for all pediatric cases of PCC/PGL [44,47]. In pediatric patients with PCC/PGL, up to 80% of cases are linked to a hereditary predisposition syndrome, such as Von Hippel-Lindau disease, multiple endocrine neoplasia type 2, neurofibromatosis type 1, and familial PGL syndromes types 1 to 5. These syndromes are caused by variants of *RET*, *VHL*, *NF1*, and *SDH* subunit genes (*SDHD*, *SDHC*, *SDHB*, *SDHA*, and *SDHAF2*) [40,47]. Early identification of germline variants after diagnosis can positively influence management and clinical outcomes of patients with heritable diseases [48].

Surgical resection remains the cornerstone of treatment for both PCC and PGL, often resulting in the remission of hypertension [40]. For children who have adrenal PCC, laparoscopic adrenalectomy is the preferred procedure, with an emphasis on partial adrenalectomy as the initial strategy when feasible [49]. The preoperative management of hypertension is critical for minimizing morbidity associated with catecholamine release and typically requires a minimum of 10 to 14 days in pediatric patients. This management includes the use of  $\alpha$ -1 receptor antagonists such as terazosin, prazosin, doxazosin, or phenoxybenzamine, and may also involve tyrosine hydroxylase inhibitors such as metyrosine. To prevent a hypertensive crisis, a regimen combining a calcium channel blocker with a  $\beta$ -blocker is recommended to counteract reflex tachycardia and prevent arrhythmias [50].

## Conclusion

Although adrenal disorders are rare, they are major causes of endocrine hypertension in children. These conditions are often associated with severe hypertension and may lead to end-organ damage at an early age if not promptly diagnosed and managed. Due to their potentially serious consequences, identifying adrenal diseases as a cause of hypertension in children is crucial for the effective treatment and prevention of long-term cardiovascular and metabolic complications. Moreover, recent advancements in genetic approaches have significantly improved our understanding of its pathophysiology, enabling more targeted management strategies by incorporating genetic information into the overall diagnostic and treatment process.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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