JEIMP
E-ISSN: 2980-0617

The Journal of
European Internal Medicine Professionals

JEIMP
The Science

Review

Diagnosis and Treatment of Monogenic Hypertension in Children

Author(s) [1]Faysal Gök, [2]Mehmet Emin Demir

Affiliation(s) [1]Medicana International Ankara Hospital, Department of Pediatric Nephrology and Rheumatology, Ankara, Turkey
[2]Atılım University, School of Medicine, Department of Nephrology, Ankara, Turkey

Corresponding Author Mehmet Emin Demir, Sogutozu Avenue, 2176. street, No: 3, 06150, Ankara, Turkey
E-mail: demirmehmetemin@hotmail.com

10.5281/zenodo.10654302

J Eur Int Prof. Year; 2024, Volume: 2, Issue: 1 *Submitted at*: 19.12.2023, *Accepted at*: 02.01.2024, *Published at*: 15.02.2024

JEIMP belongs to "*The Foundation for the Management of Chronic Diseases***" and is supervised by the MKD Digital Publishing.** www.jeimp.com and digitalmkd.com

Abstract

Hypertension (HT) is a common public health problem that develops due to primary and secondary causes. The prevalence of HT in children and adolescents is 3.6%. In childhood HT, complex and polygenic factors such as genetic, environmental, adaptive, neural, and hormonal mechanisms play a role. Among these factors, genetic factors are estimated to contribute to the development of HT by 30-60%; however, known genetic factors explain only 3% of the cases.

Monogenic inherited HT is associated with a mutation in a single gene, with or without the influence of mineralocorticoids, leading to increased sodium reabsorption and intravascular volume expansion. Typically, HT in these patients has an early onset, a family history of HT, is associated with electrolyte imbalance, and shows a clinical course refractory to treatment.

In treating monogenic inherited HT, understanding functional genetic mutations enables the utilization of highly effective pharmacogenetic pathways. This knowledge provides the opportunity to tailor treatments specifically to target the primary pathophysiological mechanism of the condition. Sodium-dependent, low renin levels, and monogenic inherited HT treatment are based on a low-sodium diet and block the pathological sodium reabsorption mechanism.

Diagnosis can be made through physical examination, blood pressure measurement, and measurement of renin, aldosterone, cortisol, and potassium levels. Monogenic inherited HTs are rare. Early diagnosis ensures blood pressure control early on, reducing the morbidity and mortality associated with HT. Genetic tests are necessary to confirm the diagnosis, make a differential diagnosis, and choose appropriate treatment.

Clinical manifestations of monogenic inherited HT in some patients extend beyond HT. Other systemic symptoms may accompany HT or manifest at certain stages of life. This article discusses monogenic inherited HT that manifests in the early stages of life, emphasizing the clinical aspects of HT.

Keywords: Hypertension, monogenic inherited, pharmacogenetics, Liddle syndrome, Geller syndrome

INTRODUCTION

Monogenic inherited hypertension (HT) syndromes refers to specific genetic mutations that interfere with normal renal and adrenal regulation of blood pressure and follows Mendelian inheritance models (1-3). In these patients, HT develops due to increased sodium reabsorption, excessive aldosterone synthesis, and enzyme deficiencies that regulate the synthesis and deactivation of adrenal steroid hormones. Clinical manifestations of HT occur as a result of intravascular volume expansion, with or without the influence of mineralocorticoids (3-5). Monogenic inherited HTs are rare. Early diagnosis is crucial for reducing the morbidity and mortality associated with HT since they can be treated (3,6-9).

The known monogenic inheritance causes of HT are characterized by abnormal sodium transport, volume expansion, and low renin in the kidneys. Several rare syndromes with monogenic inheritance that manifest with very high HT in early life have been identified (3). These include Liddle syndrome, glucocorticoid-remediable aldosteronism (GRA), apparent mineralocorticoid excess (AME), Gordon syndrome (GS), MR over-sensitivity

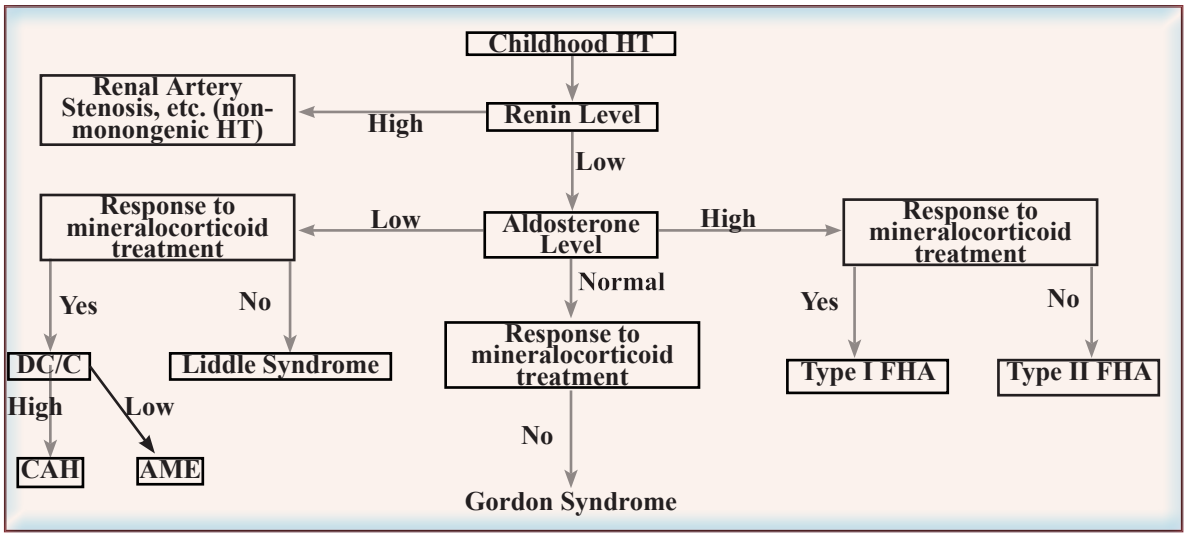

Figure 1. Diagnostic approach to childhood hypertension. DCC; deoxycortisol cortisol ratio, CAH; congenital adrenal hyperplasia, FHA; familial hyperaldosteronism (Adopted from Reference 1)

syndrome, and congenital adrenal hyperplasia (CAH). Low-renin hypertension (LRH) should be suspected in children with a family history of early-onset, severe, and resistant HT, or a history of cerebrovascular events and death due to heart failure. Hypokalemia, except in Gordon syndrome, is a common feature in most LRH cases.

EPIDEMIOLOGY

Hypertension is a significant public health problem in adults, leading to serious morbidity and mortality. The prevalence of HT is reported to be 32.6%. However, in children and adolescents, the prevalence of HT is 3.6% (1). The Human Genome Project, initiated in 2001, paved the way for large-scale genomic studies in populations. In studies conducted so far, more than 30 genes and over 1477 single-nucleotide polymorphisms (SNPs) associated with blood pressure have been identified. It is estimated that genetic factors contribute to 30-60% of the development of HT, but known genetic factors explain only 3% of hypertensive cases (2). Only a small fraction of these is related to monogenic inherited HT.

CAUSES OF MONOGENIC INHERITED HYPERTENSION

Monogenic inherited hypertension manifests in two forms, depending on its dependence on mineralocorticoids or independence (**Table 1** and **Figure 1**).

CHARACTERISTICS AND DIAGNOSIS

Monogenic inherited hypertension typically begins in early life and is characterized by a family history of hypertension. It is associated with electrolyte metabolism disorders and shows a clinical course refractory to treatment. Early diagnosis is crucial, especially in hypertensive children with a family history of early-onset hypertension. Suspicions of hypertension-related disease with a mutation in a single gene should arise, especially if plasma renin levels are suppressed, and distal tubular sodium absorption is increased. The clinical phenotypes of monogenic inherited hypertension can range from mild symptoms, including normotension or normokalemia, to life-threatening conditions. Routine mutation analysis is not always recommended in hypertensive patients' non-hypertensive siblings if renin, aldosterone, and serum electrolytes are normal.

While single-gene PCR-based tests have been successfully used in genetic identification, using whole-

Table 1. Key features of monogenic inherited hypertension types

Mineralocorticoid Dependent	Mineralocorticoid Independent
Mineralocorticoids are one of the key hormones that regulate sodium and potassium balance in the body. Single-gene inherited HT syndromes are based on the excess effect of mineralocorticoids and the resulting increase in intravascular volume. • Excessive effect of mineralocorticoids (apparent mineralocorticoid excess), • Treatable with glucocorticoids-aldosteronism (glucocorticoid-remediable aldosteronism), • Due to 11β-hydroxylase or 17α-hydroxylase deficiency (congenital adrenal hyperplasia). • Familial Hyperaldosteronism Type II-III-IV (FH-II-III-IV)	It refers to single gene inherited hypertension syndromes that develop in association with increased sodium reabsorption, independent of mineralocorticoids. • Liddle Syndrome • Gordon Syndrome

HT; hypertension, FH; familial hyperaldosteronism

genome DNA sequencing and exome sequencing is now possible for the diagnosis of rare monogenic inherited syndromes. Although the causes of monogenic inherited hypertension are rare, identifying them in childhood is beneficial for successful treatment and avoiding associated morbidity and mortality.

For diagnosis, routine physical examination, blood pressure measurement, and laboratory measurements of plasma renin activity, aldosterone, cortisol, and potassium should be performed. Genetic tests are useful for confirming the diagnosis and making a differential diagnosis. The differential diagnosis should consider secondary causes of hypertension, such as renal parenchymal diseases, renal artery stenosis, adrenal gland neoplasms, hyperthyroidism, and excessive dietary salt intake. While a definitive diagnosis in patients with a mutation in a single gene can be made through genetic analysis, in some cases, a possible diagnosis can be reached based on clinical features, laboratory results, and the response to specific pharmacological drugs (such as those with a low sodium diet and drugs blocking sodium reabsorption mechanisms).

The term "low-renin hypertension (LRH)," describing an HT phenotype with low renin activity and no prominent hyperaldosteronism, is used by the European Society of Hypertension (ESH) (6). Metabolic alkalosis is prevalent in the majority of cases, while metabolic acidosis is associated with GS (10).

Plasma Renin Activity and Aldosterone Levels: Testing and Interpretation

Plasma renin activity (PRA) and plasma aldosterone levels are measured from a blood sample taken from an upper-arm vein after the patient has been lying on their back for more than 30 minutes in the early morning, on an empty stomach. Test results can be influenced by the patient's position, specific foods, beverages, and medications, so care must be taken when collecting the blood sample. The normal daily diurnal range for plasma renin activity is 0.17–5.38 ng/mL/h, and for aldosterone, it is 2.5–39.2 ng/dL.

In cases where there are signs of increased aldosterone production, such as high blood pressure, muscle weakness, and low potassium levels, blood samples for renin activity measurement are taken from a vein in the arm. Some centers may also perform selective blood sampling from the kidneys or adrenal veins. In these patients, abnormal plasma aldosterone concentrations can be detected along with serum potassium and metabolic acid-base disorders. Normally, hypertension and low potassium levels suppress aldosterone synthesis and release.

In primary aldosteronism (PA), the most distinguishing test is the aldosterone-renin ratio (ARR). An ARR >30 (ng/dL and ng/mL/h) is indicative of the evaluation of patients with primary PA, such as familial hyperaldosteronism type I (FH-I/GRA) and familial hyperaldosteronism type II (FH-II) (10). In the case of an ARR >10 in a child with FH-I/GRA, genetic analysis is recommended (11). Genetic analysis is also suggested in cases of early-onset hypertension diagnosis and hypokalemia in a family member.

MONOGENIC INHERITED HYPERTENSION SYNDROMES

1. Apparent Mineralocorticoid Excess

AME is a rare autosomal recessive disorder characterized by high blood pressure due to a deficiency of the 11-beta-hydroxysteroid dehydrogenase type 2 (HSD11B2) enzyme in the kidneys. It has been identified in fewer than 100 patients in the last 25 years. The gene encoding HSD11B2 (HSD11B2) is located on chromosome 16q22. Mutations in the HSD11B2 gene result in insufficient synthesis of the HSD11B2 enzyme. As a consequence of the deficiency, cortisol levels rise because cortisol cannot be adequately converted to cortisone due to the lack of HSD11B2. This inappropriate activation of the mineralocorticoid receptor (MR) leads to symptoms of hyperaldosteronism (12).

Activation of MRs in renal tubule cells specifically increases sodium reabsorption through epithelial sodium channels (ENaC) and leads to an extracellular volume expansion. Cortisol has high affinity for both glucocorticoid and MRs. Consequently, low plasma renin and aldosterone levels result in hypokalemia and metabolic alkalosis (13).

These patients are often of low birth weight. Early-onset hypertension is accompanied by metabolic alkalosis and severe hypokalemia. Diagnosis can be made by the ratio of tetrahydrocortisol and allotetrahydrocortisol, metabolites of cortisol in urine, to the concentration of tetrahydrocortisone. The normal ratio is 1:1, but in AME patients, this ratio can be as high as 6.7–33. The conversion rate of cortisol to cortisone measured after cortisol infusion in AME patients is only about 0–6%, compared to what is observed in healthy individuals (14). The optimal diagnostic test can be performed with 11-tritiated cortisol injection, but this technique is not widely used due to the rarity of tritiated cortisol. Patients with AME can be treated with spironolactone and triamterene, which reduce sodium reabsorption and potassium secretion.

2. Familial Hyperaldosteronism

Familial hyperaldosteronism is characterized by early-onset hypertension accompanied by high aldosterone, low plasma renin activity, and hypokalemia. The early onset suggests an inherited cause of primary hyperaldosteronism. Four different types of familial

Table 2. A brief distinction for FH subtypes

	Genetic Variation	Pathophysiology	Presentation
Type I	CYP11B1/CYP11B2 gene	ACTH induces transcription of CYP11B2	GK-suppressive HA
Type II	CLCN2 mutation	Increased Cl^- efflux leads CYP11B2 transcription	Early-onset PA
Type III	KCNJ5 mutation	Increased NA^+ efflux leads CYP11B2 transcription	Sever early-onset PA (T158A, I157S, E145Q, G151R) Mild PA: (G151E, Y152C)
Type IV	CACNA1H mutation	Increased Ca^{2+} efflux leads CYP11B2 transcription	Early onset

CLCN2; chloride channel protein 2, KCNJ5; potassium voltage-gated channel subfamily J member 5, ACTH; adrenocorticotropic hormone, PA; primary aldosteronism, HA, GK; glucocorticoid, HA; hyper aldosteronism

hyperaldosteronism have been identified to date (Table 2).

a.Type I FH (Glucocorticoid-Remediable Aldosteronism): GRA is an autosomal dominant inherited hypertensive disorder characterized by elevated plasma aldosterone levels, low plasma renin activity, and abnormal steroid synthesis. The aldosterone synthase (CYP11B2) hyperactivity in these patients can be suppressed by glucocorticoids. It is also known as familial hyperaldosteronism type I.

Two adjacent genes, CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase), are located on chromosome 8q. The chimeric gene resulting from unequal crossovers between these two genes codes for a hybrid protein that increases aldosterone production independently of renin, due to its ability to stimulate aldosterone production (15). The chimeric gene is activated not only by low blood volume, angiotensin II, and high serum potassium levels but also by adrenocorticotropic hormone (ACTH) in these patients. Under ACTH stimulation, aldosterone is synthesized from the zona fasciculata along with cortisol. This results in a significant increase in aldosterone concentration, leading to increased potassium excretion and enhanced water reabsorption with sodium chloride (16).

GRA patients exhibit severe symptoms of hypertension along with mild hypokalemia and metabolic alkalosis. Despite low plasma renin levels, aldosterone concentrations may be normal (9). The confirmation of the diagnosis involves conducting a dexamethasone suppression test and determining the aldosterone-to-renin ratio (ARR) and hybrid steroids (18-oxocortisol and 18-hydroxycortisol) levels in urine, which helps distinguish elevated aldosterone due to ACTH influence (17). Confirmatory diagnosis often involves sequencing analysis of the chimeric CYP11B1/CYP11B2 gene.

Due to the risk of cerebral aneurysm and associated bleeding during puberty, these patients should undergo MRI angiography for monitoring (18). Treatment involves using low-dose glucocorticoids (prednisolone 2.5-5 mg/day) to suppress the stimulatory effect of ACTH on aldosterone synthesis and MR antagonist drugs such as spironolactone or eplerenone to reduce aldosterone effects. ENaC antagonists like amiloride and triamterene can also be used (19, 20). Since renin synthesis is suppressed in GRA patients, antihypertensive drugs such as ACE inhibitors and β-blockers have no role in treatment.

b.Type II FH: Pathogenic variants that functionally increase the voltage-gated chloride channel ClC-2, encoded by the chloride channel protein 2 (CLCN2) gene expressed in the zona glomerulosa layer of the adrenal gland, regulate the depolarization of the cell membrane through the activation of voltage calcium channels. This, in turn, regulates the expression of CYP11β-2, an enzyme for aldosterone biosynthesis, leading to conditions such as aldosterone-producing adenoma or idiopathic bilateral adrenal hyperplasia.

Clinical symptoms associated with FH-II-related hypertension typically develop in adulthood (21). Mutation analysis is the standard method for the definitive diagnosis of FH-II. Unlike FH-I, FH-II does not respond to glucocorticoids; therefore, in FH-II, unilateral adrenalectomy along with the use of MR antagonists is recommended for symptom improvement.

c.Type III FH-III: In FH-III, pathogenic mutations leading to functional increases in the KCNJ5 (potassium voltage-gated channel subfamily J member 5) gene result in the loss of potassium selectivity in the potassium channel of the zona glomerulosa cell. This leads to an increased influx of sodium into the cell, lowering the cell's depolarization threshold (22). Consequently, aldosterone synthesis and secretion increase in adrenal glomerulosa cells. Patients with FH-III present with severe hypertension, hypokalemia, and bilateral hyperplasia (23). In most cases, bilateral adrenalectomy is often required.

d.Type IV FH-IV: In FH-IV, pathogenic mutations leading to functional increases in the CACNA1H gene, encoding the T-type voltage-gated calcium channel Cav3.2, result in excessive calcium entry into adrenal zona glomerulosa cells, leading to hyperaldosteronism (24,25). Additionally, somatic mutations in CACNA1H, including KCNJ5, ATP1A1, and ATP2B3, have been identified in over 50% of patients with aldosterone-producing adenomas (26,27). The identification of new genetic forms in primary aldosteronism may necessitate reclassification.

3.Liddle Syndrome (Pseudo-Hyperaldosteronism)

Liddle syndrome is an autosomal dominant disorder characterized by severe hypertension, low plasma renin activity, and low plasma aldosterone levels. Mutations that lead to ENaC hyperactivity play a role in the pathogenesis of the disease.

Functional ENaC is a heterotrimer composed of α (or δ), β, and γ subunits. Each subunit has two transmembrane domains, extracellular loops or rings, and large extracellular loops. ENaC in the kidneys is primarily expressed in the principal cells of the aldosterone-sensitive distal nephron. These cells are found in the distal convoluted tubule, connecting tubule, and collecting duct, where hormonally controlled, rate-limiting sodium reabsorption occurs. Increases in ENaC activity lead to inappropriate sodium retention, while decreases in activity result in natriuresis and diuresis. ENaC activity is regulated by various factors, including aldosterone. In principal cells, aldosterone activates MR to "upregulate" the positive regulators of the channel. Aldosterone also causes a trophic increase in ENaC transcription through the MR pathway.

In Liddle syndrome, mutations in the SCNN1A, SCNN1B, and SCNN1G genes, encoding the α, β, and γ subunits of ENaC, respectively, result in changes that confer hyperfunction to ENaC. Mutations in the β and γ subunits cause the carboxy terminus (early stop codon) of the ENaC molecule it encodes to be shortened due to heterozygous mutations in the SCNN1B and/or SCNN1G genes in LS. Since the mutant ENaC protein lacks the Nedd 4-2 binding region, it cannot be tagged for metabolism. In these patients, ENaC sodium sensitivity and sodium reabsorption are increased independently of the effects of mineralocorticoids (28-31).

In LS, early-onset salt-sensitive hypertension, hypokalemia, metabolic alkalosis, low PRA, and low aldosterone levels are detected. Urinary potassium concentration is high, and sodium levels are low in these patients. Treatment for hypertension involves a salt-free or low-sodium diet and the use of potassium-sparing diuretics, such as amiloride or triamterene, with direct inhibition of ENaC. MR inhibitors like spironolactone have no place in the treatment.

4. Gordon Syndrome (Pseudo-Hypoaldosteronism/ Hypoaldosteronism Type 2)

Gordon syndrome is a rare inherited form of monogenic hypertension associated with hyperkalemia and metabolic acidosis. After its recognition in the 1960s, a phenotype-genotype correlation was observed in families with Gordon syndrome, and subsequently, four genes, WNK1, WNK4, KLHL3, and CUL3, were shown to play a role in the disease pathogenesis. The encoded proteins Kelch-like 3 and Cullin 3 interact to form a ring-like complex with WNK-kinase 4. This interaction, under normal conditions, inhibits the renal outer medullary potassium channel (ROMK) by affecting the sodium-chloride cotransporter (NCC) and ENaC, promoting normokalemia and normotension. WNK-kinase 1 has an inhibitory effect on WNK-kinase 4. Mutations in WNK1, WNK4, KLHL3, and CUL3, all result in the accumulation of WNK-kinase 4, leading to hypertension, hyperkalemia, and metabolic acidosis (35-38). Only a small fraction of patients with GS have been associated with mutations in WNK1 and WNK4. Hypertension associated with mutations in the CUL3 gene emerges early and is much more severe; it progresses with profound acidosis and severe hyperkalemia (38).

The clinical phenotype of patients with GS is the same for mutations in any of the four proteins (WNK1, WNK4, CUL3, and KLHL3), and similar electrolyte imbalances are observed. Affected individuals initially present with hyperkalemia, normal serum sodium levels, hyperchloremic metabolic acidosis, and hypercalciuria. Plasma renin activity is suppressed, and aldosterone levels are incongruently low with hyperkalemia. Chronic mineralocorticoid-resistant hyperkalemia and hypertension are observed. The sodium-chloride cotransporter is located on the apical surface of the distal tubule; it facilitates the reabsorption of 5-10% of filtered NaCl and is inhibited by thiazide. Treatment with thiazide diuretics dramatically improves electrolyte abnormalities and blood pressure by inhibiting NCC (39,40).

5. Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH), an autosomal recessive disorder caused by mutations in the CYP11B1 and CYP17A1 genes associated with cortisol biosynthesis. CYP11B1 and CYP17A1 code for 11β-hydroxylase and 17α-hydroxylase, respectively. Deficiency in either 11β-hydroxylase or 17α-hydroxylase leads to the excessive production of 21-hydroxylated steroid intermediates with mineralocorticoid effects, resulting in hypertension (5). The overproduction of these intermediates is due to increased ACTH production resulting from the loss of the negative feedback effect of cortisol (41). Elevated levels of 11-deoxycorticosterone

(DOC) lead to excessive MR activation and low renin activity. In girls with 17α-hydroxylase deficiency, impaired steroidogenesis occurs in both the adrenals and gonads, leading to the absence of secondary sexual characteristics and amenorrhea. Depending on the severity of mutations, patients with 11β-hydroxylase deficiency may present with genital ambiguity, hirsutism, premature bone maturation, and early puberty (42).

Virilization, a phenotypic manifestation of CYP11B1 deficiency, may also develop due to excessive androgen production, depending on the severity of the mutations and the presence of the CYP11B/β1 hybrid gene resulting from recombination between the CYP11B2 and CYP11B1 genes.

Diagnosis is typically based on clinical symptoms, and confirmation is achieved through mutation studies for 11β-hydroxylase and 17α-hydroxylase. Affected individuals show early-onset hypertension, hypernatremia, hypokalemia, and low renin activity. Treatment for hypertension involves the use of the MR antagonist spironolactone and dexamethasone.

In the most common cause of KAH, 21-hydroxylase deficiency, unlike deficiencies in 11β-hydroxylase and 17α-hydroxylase, there is sodium loss, and hypertension does not develop.

6. Familial Glucocorticoid Resistance

Inactivating mutations in the NR3C1 gene, located in the chromosomal region 5q31-q32, can lead to familial glucocorticoid resistance, and they can be inherited in both autosomal recessive and dominant patterns. Mutant glucocorticoid receptors (GRs) fail to respond to cortisol (43,44). Consequently, there is an increase in cortisol and ACTH levels. Due to elevated ACTH, there is an overproduction of mineralocorticoids and androgens. Cortisol has a high affinity for both glucocorticoid and MRs. In these patients, in addition to an increase in mineralocorticoids, there is also MR activation in renal tubules mediated by hypercortisolism. Clinical findings include hypertension, hypokalemia, low renin and aldosterone levels, hirsutism, and precocious puberty in females (45). Affected individuals do not develop a Cushingoid appearance due to GRs insensitivity. These patients are diagnosed with high cortisol levels through genetic analysis.

Nightly low-dose dexamethasone treatment suppresses ACTH secretion and corrects excessive glocorticoids, hypercortisolism, and hyperandrogenism. MR antagonists such as spironolactone and eplerenone are effective in controlling hypertension in individuals with familial glucocorticoid resistance.

7. Geller Syndrome

Hypertension resulting from a heterozygous mutation in the MR, due to changes in ligand selectivity and activation of the nuclear receptor, is known as Geller Syndrome (46,47). Normally, both the GRs and MR have high affinity for cortisol due to their structural similarities (48). However, aldosterone exhibits a clear MR specificity. In healthy individuals, cortisol activation of MR is prevented by the conversion of cortisol to cortisone.

In Geller syndrome, the mutant MR shows increased sensitivity to other steroid hormones like progesterone. In females with a heterozygous MR mutation, hypertension develops during pregnancy due to elevated progesterone levels and increased MR sensitivity. In males with a heterozygous MR mutation, cortisol binds to MR with sensitivity comparable to aldosterone, resulting in hypertension (49).

These patients typically present with hypertension at a young age, decreased plasma renin activity (PRA), and low serum aldosterone levels. When progesterone levels rise significantly during pregnancy, this mutation can lead to severe hypertension. Patients with Geller syndrome must adhere to a low-salt diet, and their pregnancy should be closely monitored. Spironolactone has alternative binding sites on MR, and binding to these sites (MRL810 alternative binding parameter) can cause spironolactone to exert a severe agonistic effect, leading to electrolyte imbalance and hypertension (paradoxical activation) (8).

8. Brachydactyly Autosomal Dominant Hypertension (ODHB)

ODHB is a condition characterized by autosomal dominant inheritance due to a mutation in the PDE3A gene. Individuals with ODHB typically exhibit short stature, hypertension that progresses with age independently of salt intake, and altered baroreflex regulation (50,51). Additionally, affected individuals show thickening and shortening of metacarpals and phalanges, characterized by typical E brachydactyly (52,53). If hypertension is left untreated, it often leads to cerebral hemorrhage, resulting in death usually before the age of 50.

The PDE3A gene is located on chromosome 12 and encodes phosphodiesterase 3A (PDE3A), a member of the cyclic nucleotide phosphodiesterase (cGI-PDE) family inhibited by c-GMP. Functional analyses have shown that mutations in PDE3A increase protein kinase A-mediated phosphorylation of PDE3A. The mutation-related increase in PDE3A activity leads to enhanced cAMP hydrolysis and reduced cAMP levels. The increased cAMP hydrolysis causes a decrease in phosphoprotein levels stimulated by phosphorylated vasodilators. Hypertension results from vasoconstriction and increased peripheral vascular resistance associated with these changes.

Clinical manifestations develop due to the mutation causing a functional increase in PDE3A in the gene. These mutations contribute to hypertension by increasing peripheral vascular resistance, accompanied by characteristic skeletal changes. Affected individuals are not sensitive to salt, and they exhibit normal renin, aldosterone, and catecholaminergic responses to decreased and increased vascular volume.

Hypertension emerges in childhood and progresses over time. Diagnosis typically occurs in childhood, and early treatment can reduce the likelihood of stroke (55). Studies have demonstrated significant reductions in hypertension with the use of antihypertensive drugs, beta-blockers, alpha-blockers, calcium channel blockers, and ACE inhibitors, either in combination or as monotherapy (56). Research is ongoing to explore measures aimed at increasing cGMP to address cAMP deficiency.

9. Familial Pheochromocytoma

In individuals with familial pheochromocytoma, specific mutations are identified, leading to severe paroxysmal hypertension attacks with elevated levels of epinephrine and norepinephrine. It can be associated with various syndromes. Von Hippel-Lindau disease is linked to bilateral pheochromocytomas, retinal and cerebellar angiomas, kidney, and pancreatic cysts, and renal cell carcinoma. The mutation causing this disease has been identified on 3p25.3, and it is also a tumor suppressor gene defect (57). RET, a proto-oncogene, is associated with non-syndromic pheochromocytoma as well as multiple endocrine neoplasia syndrome type 2 (MEN 2). MEN 2 is an autosomal dominantly inherited disorder due to a mutation on chromosome 10q11.21. MEN 2 has two subtypes: MEN 2A, associated with pheochromocytoma, medullary thyroid carcinoma, and hyperparathyroidism; and MEN 2B, associated with pheochromocytoma, medullary thyroid carcinoma, and mucosal neuromas. Pheochromocytoma is also linked to neurofibromatosis type I caused by mutations in the NF1 gene located on chromosome 17q11.2. Studies have shown that solitary pheochromocytomas may contain mutations in the mentioned genes. A study on solitary tumors reported that 86% of them included copy number alterations in genes associated with familial pheochromocytoma, with NF1 alterations being the most common in 26% of the tumors (59).

Initially, it was believed that 10% of pheochromocytomas were familial, and 90% were sporadic. New technology in genetic testing has revealed that 50% of pheochromocytomas are sporadic, and 15-25% are associated with germ line mutations (60).

According to the Endocrine Society clinical practice guidelines, the treatment for functional pheochromocytomas involves initiating antihypertensive therapy followed by tumor resection. Treatment should begin with alpha-adrenergic antagonists (e.g., phenoxybenzamine or doxazosin) before surgery. Other antihypertensives, especially dihydropyridines and beta-adrenergic antagonists, may be used additionally. Blood pressure and catecholamine metabolism should be carefully monitored throughout the perioperative process. Due to the association of pheochromocytoma with various neoplastic syndromes mentioned above, genetic testing may be recommended as a prognostic and preventive indicator (61).

CONCLUSION

In conclusion, monogenic inherited hypertension in children presents a complex interplay of genetic, environmental, and hormonal factors. While the prevalence of hypertension in children is relatively low, understanding and diagnosing monogenic forms are crucial for effective management. Genetic testing plays a pivotal role in confirming diagnoses and guiding tailored treatments, targeting the specific genetic mutations underlying these conditions.

Early identification of monogenic hypertension allows for the implementation of targeted therapeutic strategies, including low-sodium diets and drugs that address the pathological sodium reabsorption mechanisms. Additionally, recognizing associated syndromes and manifestations beyond hypertension is essential for comprehensive patient care.

Despite the rarity of these monogenic inherited forms, their impact on morbidity and mortality emphasizes the importance of early intervention. Ongoing research and advancements in genetic testing contribute to our understanding of these conditions, paving the way for improved diagnostic accuracy and therapeutic options. In the realm of pediatric hypertension, a multidisciplinary approach that integrates clinical, genetic, and pharmacogenetic insights is essential for optimizing patient outcomes and reducing the long-term consequences of monogenic hypertension.

DECLARATIONS

Financial Disclosure: This article does not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: None

Informed consent form: Not available

Funding source: No funding was received for the research

REFERENCES

1. Raina R, Krishnappa V, Das A, et al. Overview of Monogenic or Mendelian Forms of Hypertension. *Front Pediatr.* 2019;7:263. Published 2019 Jul 1. doi:10.3389/fped.2019.00263
2. Ahn SY, Gupta C. Genetic Programming of Hypertension. *Front Pediatr.* 2018;5:285. Published 2018 Jan 22. doi:10.3389/fped.2017.00285
3. Singh V, Van Why SK. Monogenic Etiology of Hypertension. *Med Clin North Am.* 2024;108(1):157-172. doi:10.1016/j.mcna.2023.06.005

4. Park SJ, Shin JI. Diagnosis and Treatment of Monogenic Hypertension in Children. *Yonsei Med J.* 2023;64(2):77-86. doi:10.3349/ymj.2022.0316
5. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell*. 2001;104(4):545-556. doi:10.1016/s0092-8674(01)00241-0
6. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens*. 2016;34(10):1887-1920. doi:10.1097/HJH.0000000000001039
7. Precone V, Krasi G, Guerri G, et al. Monogenic hypertension. *Acta Biomed.* 2019;90(10-S):50-52. Published 2019 Sep 30. doi:10.23750/abm.v90i10-S.8759
8. Levanovich PE, Diaczok A, Rossi NF. Clinical and Molecular Perspectives of Monogenic Hypertension. *Curr Hypertens Rev.* 2020;16(2):91-107. doi:10.2174/1573402115666190409115330
9. Aggarwal A, Rodriguez-Buritica D. Monogenic Hypertension in Children: A Review With Emphasis on Genetics. *Adv Chronic Kidney Dis.* 2017;24(6):372-379. doi:10.1053/j.ackd.2017.09.006
10. Vehaskari VM. Heritable forms of hypertension. *Pediatr Nephrol.* 2009;24(10):1929-1937. doi:10.1007/s00467-007-0537-8
11. Garovic VD, Hilliard AA, Turner ST. Monogenic forms of low-renin hypertension. *Nat Clin Pract Nephrol.* 2006;2(11):624-630. doi:10.1038/ncpneph0309
12. Yau M, Haider S, Khattab A, et al. Clinical, genetic, and structural basis of apparent mineralocorticoid excess due to 11β-hydroxysteroid dehydrogenase type 2 deficiency. *Proc Natl Acad Sci U S A.* 2017;114(52):E11248-E11256. doi:10.1073/pnas.1716621115
13. Choi KB. Hypertensive hypokalemic disorders. *Electrolyte Blood Press.* 2007;5(1):34-41. doi:10.5049/EBP.2007.5.1.34
14. Palermo M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: an overview. *Arq Bras Endocrinol Metabol*. 2004;48(5):687-696. doi:10.1590/s0004-27302004000500015
15. Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature*. 1992;355(6357):262-265. doi:10.1038/355262a0
16. Fisher A, Friel EC, Bernhardt R, et al. Effects of 18-hydroxylated steroids on corticosteroid production by human aldosterone synthase and 11beta-hydroxylase. *J Clin Endocrinol Metab.* 2001;86(9):4326-4329. doi:10.1210/jcem.86.9.7797
17. Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. *Endocrinol Metab Clin North Am.* 2002;31(3):619-xi. doi:10.1016/s0889-8529(02)00013-0
18. Levanovich PE, Diaczok A, Rossi NF. Clinical and Molecular Perspectives of Monogenic Hypertension. *Curr Hypertens Rev.* 2020;16(2):91-107. doi:10.2174/1573402115666190409115330
19. Litchfield WR, Anderson BF, Weiss RJ, Lifton RP, Dluhy RG. Intracranial aneurysm and hemorrhagic stroke in glucocorticoid-remediable aldosteronism. *Hypertension*. 1998;31(1 Pt 2):445-450. doi:10.1161/01.hyp.31.1.445
20. Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(5):1889-1916. doi:10.1210/jc.2015-4061
21. Stowasser M, Gordon RD. Primary aldosteronism--careful investigation is essential and rewarding. *Mol Cell Endocrinol.* 2004;217(1-2):33-39. doi:10.1016/j.mce.2003.10.006
22. Geller DS, Zhang J, Wisgerhof MV, Shackleton C, Kashgarian M, Lifton RP. A novel form of human mendelian hypertension featuring nonglucocorticoid-remediable aldosteronism. *J Clin Endocrinol Metab.* 2008;93(8):3117-3123. doi:10.1210/jc.2008-0594
23. Choi M, Scholl UI, Yue P, et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science*. 2011;331(6018):768-772. doi:10.1126/science.1198785
24. Korah HE, Scholl UI. An Update on Familial Hyperaldosteronism. *Horm Metab Res.* 2015;47(13):941-946. doi:10.1055/s-0035-1564166
25. Daniil G, Fernandes-Rosa FL, Chemin J, et al. CACNA1H Mutations Are Associated With Different Forms of Primary Aldosteronism. *EBioMedicine*. 2016;13:225-236. doi:10.1016/j.ebiom.2016.10.002
26. Fernandes-Rosa FL, Williams TA, Riester A, et al. Genetic spectrum and clinical correlates of somatic mutations in aldosterone-producing adenoma. *Hypertension*. 2014;64(2):354-361. doi:10.1161/HYPERTENSIONAHA.114.03419
27. Monticone S, Else T, Mulatero P, Williams TA, Rainey WE. Understanding primary aldosteronism: impact of next generation sequencing and expression profiling. *Mol Cell Endocrinol.* 2015;399:311-320. doi:10.1016/j.mce.2014.09.015
28. Shimkets RA, Warnock DG, Bositis CM, et al. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell*. 1994;79(3):407-414. doi:10.1016/0092-8674(94)90250-x
29. Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet.* 1995;11(1):76-82. doi:10.1038/ng0995-76
30. Snyder PM, Price MP, McDonald FJ, et al. Mechanism by which Liddle's syndrome mutations increase activity of a human epithelial Na+ channel. *Cell*. 1995;83(6):969-978. doi:10.1016/0092-8674(95)90212-0
31. Salih M, Gautschi I, van Bemmelen MX, et al. A Missense Mutation in the Extracellular Domain of αENaC Causes Liddle Syndrome. *J Am Soc Nephrol.* 2017;28(11):3291-3299. doi:10.1681/ASN.2016111163
32. Monnens L, Levtchenko E. Distinction between Liddle syndrome and apparent mineralocorticoid excess. *Pediatr Nephrol.* 2004;19(1):118-119. doi:10.1007/s00467-003-1311-1
33. Nesterov V, Krueger B, Bertog M, Dahlmann A, Palmisano R, Korbmacher C. In Liddle Syndrome, Epithelial Sodium Channel Is Hyperactive Mainly in the Early Part of the Aldosterone-Sensitive Distal Nephron. *Hypertension*. 2016;67(6):1256-1262. doi:10.1161/HYPERTENSIONAHA.115.07061
34. Furuhashi M, Kitamura K, Adachi M, et al. Liddle's syndrome caused by a novel mutation in the proline-rich PY motif of the epithelial sodium channel beta-subunit. *J Clin Endocrinol Metab.* 2005;90(1):340-344. doi:10.1210/jc.2004-1027
35. Gordon RD. Syndrome of hypertension and hyperkalemia with normal glomerular filtration rate. *Hypertension*. 1986;8(2):93-102. doi:10.1161/01.hyp.8.2.93
36. Pathare G, Hoenderop JG, Bindels RJ, San-Cristobal P. A molecular update on pseudohypoaldosteronism type II. *Am J Physiol Renal Physiol.* 2013;305(11):F1513-F1520. doi:10.1152/ajprenal.00440.2013
37. Wilson FH, Disse-Nicodème S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science*. 2001;293(5532):1107-1112. doi:10.1126/science.1062844.
38. Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature*. 2012;482(7383):98-102. Published 2012 Jan 22. doi:10.1038/nature10814
39. Licht JH, Amundson D, Hsueh WA, Lombardo JV. Familiar hyperkalaemic acidosis. *Q J Med.* 1985;54(214):161-176.
40. Schambelan M, Sebastian A, Rector FC Jr. Mineralocorticoid-resistant renal hyperkalemia without salt wasting (type II pseudohypoaldosteronism): role of increased renal chloride reabsorption. *Kidney Int.* 1981;19(5):716-727. doi:10.1038/ki.1981.72
41. Portrat S, Mulatero P, Curnow KM, Chaussain JL, Morel Y, Pascoe L. Deletion hybrid genes, due to unequal crossing over between CYP11B1 (11beta-hydroxylase) and CYP11B2(aldosterone synthase) cause steroid 11beta-hydroxylase deficiency and congenital adrenal hyperplasia. *J Clin Endocrinol Metab.* 2001;86(7):3197-3201. doi:10.1210/jcem.86.7.7671
42. Sahakitrungruang T. Clinical and molecular review of atypical congenital adrenal hyperplasia. *Ann Pediatr Endocrinol Metab.* 2015;20(1):1-7. doi:10.6065/apem.2015.20.1.1
43. Yang N, Ray DW, Matthews LC. Current concepts in glucocorticoid resistance. *Steroids*. 2012;77(11):1041-1049. doi:10.1016/j.steroids.2012.05.007
44. Vitellius G, Fagart J, Delemer B, et al. Three Novel Heterozygous Point Mutations of NR3C1 Causing Glucocorticoid Resistance. *Hum Mutat.* 2016;37(8):794-803. doi:10.1002/humu.23008
45. van Rossum EF, Lamberts SW. Glucocorticoid resistance syndrome: A diagnostic and therapeutic approach. *Best Pract Res Clin Endocrinol Metab.* 2006;20(4):611-626. doi:10.1016/j.beem.2006.09.005
46. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science*. 2000;289(5476):119-123. doi:10.1126/science.289.5476.119
47. Moras D, Gronemeyer H. The nuclear receptor ligand-binding domain: structure and function. *Curr Opin Cell Biol.* 1998;10(3):384-391. doi:10.1016/s0955-0674(98)80015-x
48. Baker ME. Adrenal and sex steroid receptor evolution: environmental implications. *J Mol Endocrinol.* 2001;26(2):119-125. doi:10.1677/jme.0.0260119
49. Hellal-Levy C, Couette B, Fagart J, Souque A, Gomez-Sanchez C, Rafestin-Oblin M. Specific hydroxylations determine selective corticosteroid recognition by human glucocorticoid and mineralocorticoid receptors. *FEBS Lett.* 1999;464(1-2):9-13. doi:10.1016/s0014-5793(99)01667-1
50. Naraghi R, Schuster H, Toka HR, et al. Neurovascular compression at the ventrolateral medulla in autosomal dominant hypertension and brachydactyly. *Stroke*. 1997;28(9):1749-1754. doi:10.1161/01.str.28.9.1749
51. Schuster H, Toka O, Toka HR, et al. A cross-over medication trial for patients with autosomal-dominant hypertension with brachydactyly. *Kidney Int.* 1998;53(1):167-172. doi:10.1046/j.1523-1755.1998.00732.x
52. Wakabayashi S, Tsutsumimoto T, Kawasaki S, Kinoshita T, Horiuchi H, Takaoka K. Involvement of phosphodiesterase isozymes in osteoblastic differentiation. *J Bone Miner Res.* 2002;17(2):249-256. doi:10.1359/jbmr.2002.17.2.249
53. Maass PG, Aydin A, Luft FC, et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. *Nat Genet.* 2015;47(6):647-653. doi:10.1038/ng.3302
54. Maurice DH, Palmer D, Tilley DG, et al. Cyclic nucleotide phosphodiesterase activity, expression, and targeting in cells of the cardiovascular system. *Mol Pharmacol.* 2003;64(3):533-546. doi:10.1124/mol.64.3.533
55. Toka O, Maass PG, Aydin A, et al. Childhood hypertension in autosomal-dominant hypertension with brachydactyly. *Hypertension*. 2010;56(5):988-994. doi:10.1161/HYPERTENSIONAHA.110.156620
56. Toka O, Tank J, Schächterle C, et al. Clinical effects of phosphodiesterase 3A mutations in inherited hypertension with brachydactyly. *Hypertension*. 2015;66(4):800-808. doi:10.1161/HYPERTENSIONAHA.115.06000

57. Neumann HP, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. *Lancet*. 1991;337(8749):1052-1054. doi:10.1016/0140-6736(91)91705-y
58. Ishizaka Y, Itoh F, Tahira T, et al. Human ret proto-oncogene mapped to chromosome 10q11.2. *Oncogene*. 1989;4(12):1519-1521.
59. Welander J, Larsson C, Bäckdahl M, et al. Integrative genomics reveals frequent somatic NF1 mutations in sporadic pheochromocytomas. *Hum Mol Genet.* 2012;21(26):5406-5416. doi:10.1093/hmg/dds402
60. Kaplan NM, Victor RG. *Kaplan's Clinical Hypertension*. Philadelphia, PA: Lippincott Williams and Wilkins (2009).
61. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2023 Apr 13;108(5):e200]. *J Clin Endocrinol Metab.* 2014;99(6):1915-1942. doi:10.1210/jc.2014-1498