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A narrative review of Hyporeninemic hypertension—an indicator for monogenic forms of hypertension

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Abstract

Background and Objective: While the role of the renin-angiotensin-aldosterone system (RAAS) in the development of hypertension is well known, the significance and contribution of low renin hypertension is often overlooked. RAAS stimulation results in more tubular absorption of sodium and water along the nephron, contributing to a higher circulating vascular volume. In addition, members of the RAAS system, such as angiotensin II, have direct effects on vascular vasoconstriction, the heart, aldosterone synthesis in the adrenal glands, the sympathetic nervous system, and the central nervous system. This has resulted in a line of antihypertensive therapeutics targeting RAAS with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and renin inhibitors, which prevent conversion of angiotensinogen to angiotensin. While general practitioners and nephrologists are well aware of the causes and the long-term consequences of elevated renin and aldosterone levels, the opposite situation with low renin and/or low aldosterone levels is frequently underappreciated. The objective of this review is to provide insight to the less common forms of hyporeninemic hypertension.

Methods: We searched the PubMed online library for keywords related to hyporeninemic hypertension and focused on the pediatric population. For pathophysiology we focused on literature of the last 5 years.

Key Content and Findings: The low renin and aldosterone levels may be indicators of inherited (especially when associated with hypokalemia), monogenic forms of hypertension

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stimulating excessive tubular sodium and water absorption which subsequently results in plasma volume expansion and hypertension. These forms of hypertension require frequently specific forms of therapy. This underlines the importance of the practitioner to be familiar with these rare diseases.

Conclusions: In this review article, we outline the different forms of hypertension characterized by low renin/low aldosterone and low renin/high aldosterone levels, how to diagnose these forms of hypertension, and how to treat them.

Keywords

Hyporeninemia; hypertension; inheritance; genetics; aldosterone

Introduction

Hypertension is one of the leading causes of morbidity and mortality among adults with an estimated prevalence of 1.1 billion worldwide contributing to over 7 million deaths (1–6). Although the adverse outcomes of hypertension such as cardiovascular disease, stroke, and kidney disease usually manifest during adulthood, high blood pressure during childhood is progressive and one of the strongest predictors of adulthood hypertension in the future (7–9). High blood pressure in children is defined based on the child's age, sex, and height according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents which was published in 2004 (10) and revised in 2017 (11). The prevalence of hypertension ranges from 2.2% to 11.4% in the general pediatric population (12,13) up to 24.8% in high-risk groups such as obese patients or kidney patients (14).

Primary hypertension is polygenic and results from complex interactions among different genes and environmental factors (15). On the other hand, secondary hypertension can be caused by a large number of different conditions that can be either acquired secondary to medications or related to renovascular, endocrine, oncologic, or neurological problems (16) (Table 1). There is a subcategory of secondary hypertension characterized by low renin and are referred to as hyporeninemic hypertension or low-renin hypertension (17) (Table 2). These forms of hypertension are caused by pathogenic variants in a single gene and are referred to as monogenic hypertension (18). Most of these genes are involved in the renal and adrenal regulation of blood pressure and intravascular volume. The net result of these mutations lead to either one or more of the following mechanisms: (I) increased mineralocorticoid synthesis, (II) increased response to normal/low mineralocorticoid levels, and (III) excessive sodium (Na^+) reabsorption at the level of the nephrons. All three mechanisms result in volume excess and inability to excrete excess sodium (19). Recent advancement in genetic studies revealed that this form of hypertension is underdiagnosed in patients with hypertension (20,21). Unfortunately, the suppressed levels of renin and/or aldosterone are often overlooked and underappreciated as indicators for forms of monogenic hypertension. Moreover, the aldosterone-to-renin ratio provides an indicator of aldosterone excess even in patients with normal aldosterone levels (22). Importantly, once the specific cause is identified targeted treatment may allow for much better controlled blood pressures. The identification of hyporeninemic hypertension and then the correct diagnosis of the

specific condition are crucial for the appropriate treatment. In this article, we outline the different conditions, their genetic causes, how to diagnose them, and how to treat the specific conditions.

Methods

We searched publications in PubMed online (www.pubmed.org) using title and abstract keywords “hyporeninemic hypertension”, “low renin hypertension”, “Liddle Syndrome”, “Gordon Syndrome”, “Apparent Mineralocorticoid Excess”, “Geller Syndrome”, “hypertension exacerbated by pregnancy”, “Glucocorticoid Remediable Aldosteronism”, “Familial Hyperaldosteronism”, “monogenic hypertension”, “inherited hypertension”, “genetic hypertension” (Table 3). We focused our search on the pediatric population. For literature on pathophysiology, we focused our search on the past 5 years. For the different syndromes, we referred to the original studies that provided early characterization of the disease.

The renin-angiotensin-aldosterone system (RAAS)

The RAAS system has been extensively studied for its role in maintaining fluid homeostasis and blood pressure control (23). Upregulation of renin and aldosterone activity due to renal scarring, frequent UTIs, and chronic kidney disease is a major cause for hypertension with kidney disease (24). In addition to fluid balance and blood pressure control, RAAS plays an important role in chronic kidney disease progression (25), cardiovascular remodeling (26), activation of the thirst center and sympathetic nervous system (27), obesity and metabolic syndrome, inflammation and immune activation (18), lung (28), and liver fibrosis (29). Renin is an aspartyl-protease produced by the juxtaglomerular cells and the collecting duct. It converts angiotensinogen, a 14 amino acid peptide produced mainly in the liver, into angiotensin I (Ang-I), a 10 amino acid peptide (30). Renin secretion is regulated by mechanisms that reflect changes in blood volume and subsequently glomerular filtration (31). This includes the kidney baroreflex and chloride (Cl^-) delivery at the level of the macula densa in addition to vasoactive molecules such as nitric oxide, adenosine, and prostaglandins (32). Ang-I has several ensuing fates that depend on the type of angiotensin converting enzymes present. This has been thoroughly reviewed by Silva *et al.* in the paper discussing the interaction of RAAS with coronavirus (33). In the classical pathway, Ang-I is cleaved by angiotensin converting enzyme (ACE), a dicarboxypeptidase located on the surface of endothelial cells mainly in the pulmonary and intestinal capillaries (34), into an 8 amino acid peptide angiotensin II (Ang-II). Ang-II is the effector molecule of the classical pathway. It has opposing effects depending on the receptor it binds to. Activation of angiotensin receptor type 1 (AT1R) will overall lead to increase in blood pressure, sodium retention, inflammation, remodeling, and fibrosis mediated by vasoconstriction, stimulation of aldosterone production and anti-diuretic hormone (ADH) production, and activation of sympathetic nervous system (SNS) tone (26). On the other hand, activation of the Angiotensin Receptor type 2 (AT2R) has an opposite effect that results in lowering blood pressure and increased sodium excretion. However, AT2R expression is significant during fetal development and early neonatal life (31). In the alternative pathway, Ang-I is cleaved by ACE2, a monocarboxypeptidase integral membrane protein (35). ACE2 is

cleaved by ADAM17, a metalloprotease, and released into the blood stream. It cleaves Ang-I to generate Ang-(1–7), a heptapeptide, that preferentially binds to the Mas receptor (28). Although the downstream molecular pathways of Mas receptor activation are not fully understood, most of the experimental studies showed an overall counter Ang-II effect including vasodilation, decreased aldosterone and anti-diuretic hormone production, decreased inflammation and reactive oxygen species production (36,37). Due to the COVID-19 pandemic, ACE2 has gained attention in the scientific community (38). ACE2 acts as viral receptor for COVID-19. The binding of the virus leads to ACE2 entry into the cell rendering the enzyme unavailable to counter the ACE effect (39). The imbalance between Ang-(1–7) and Ang II is associated with disease severity and seems to play a role in ARDS commonly seen in severe COVID-19 infection (40,41).

Work up for hypertension

It may seem difficult to decide which child to work up for hypertension. Although the prevalence of inherited hypertension is unknown and thought to be rare, there are increasing numbers of reports about patients with inherited hypertension (42) (Table 2). With this manuscript, we attempt to increase the sensitivity and suspicion of the general provider. The level of scrutiny may be low as children with inherited forms of hypertension may initially present without severe hypertension and the associated electrolyte disorders may be absent. Work-up of hypertension starts with a good history and physical exam. The history should focus on prematurity, pain, medications, snoring (as obstructive sleep apnea also contributes to hypertension), and very importantly the family history. The family history should not only include kidney disease, hypertension, and need for a kidney transplant but also myocardial infarctions, aortic aneurysms, and strokes (16). In our opinion, an adolescent patient with a stroke and a positive family history of hypertension should undergo a thorough work-up.

Laboratory work up should include a urinalysis, chemistry panel including electrolytes, BUN, and creatinine, lipid profile (fasting), HgbA1c, liver enzymes, TSH, T4, cortisol (morning level), renin, aldosterone, and CBC (11,24). The hyperkalemia linked with Gordon syndrome is not always present (43). Hypokalemia is only diagnosed in 50% of glucocorticoid-remediable aldosteronism (GRA) (44) and is not persistently diagnosed in all patients with apparent mineralocorticoid excess (AME) (45) or Liddle's syndrome (46). In most of the inherited forms of hypertension mild metabolic alkalosis is detected except for Gordon syndrome which usually is associated with metabolic acidosis. Urine electrolytes are not helpful in the diagnosis. Perhaps the most useful tools in the detection of inherited forms of hypertension are the renin and aldosterone levels (47). Preferably, these parameters should be obtained prior to therapy, in particular when an ACE inhibitor or ARB is used. A helpful tool to assess for increased aldosterone activity is the plasma aldosterone (ng/dL)-to-plasma renin activity (ng/mL/h) ratio, which is an indicator for excess aldosterone even in the context of a normal plasma aldosterone level. An aldosterone-to-renin ratio above 30 is consistent with primary aldosteronism (PA) (48). Additional tests may include a drug screen if there is suspicion for substance abuse. A renal ultrasound may detect cystic kidney disease or a renal mass.

Hyporeninemic hypertension

These patients constitute a group of individuals who have been excluded to have common causes of hypertension such as renovascular hypertension, kidney disease, coarctation of the aorta, pheochromocytoma, or hyperthyroidism (Table 1). In the past, the cause for the suspected hypertension remained unclear but with improved genetic testing inherited causes of hypertension have become better understood and are often characterized by hyporeninemia. While idiopathic or primary hypertension is often thought to be polygenic in origin hyporeninemic hypertension is frequently inherited due to a single gene mutation in a Mendelian fashion (48–50). Progress made in molecular genetics over the last 40 years resulted in the identification of a number of hyporeninemic conditions which have improved our understanding of the pathophysiology and have allowed for the development of targeted treatments. Some of these initially considered rare conditions have proven to be more common and should be considered in hypertensive children (15), especially given a positive family history of hypertension, stroke, or end-stage kidney disease. A typical feature of these inherited forms of hypertension is a suppressed low renin level due to expanded extracellular volume as a consequence from inappropriate Na^+ absorption in the distal nephron. This is consistent with the hypothesis that dysfunctional mechanisms to regulate Na^+ and volume balance due to impaired renal natriuresis is part of the pathomechanism of hypertension (51,52).

The different modalities of Na^+ transport in the distal nephron

At the root of many forms of hyporeninemic hypertension is overstimulation of Na^+ absorption in the distal nephron. There are two sites for Na^+ absorption in the distal nephron, the distal convoluted tubule (DCT) and the collecting duct (CD) (48). In the DCT Na^+ enters the apical thiazide-sensitive sodium-chloride-cotransporter (NCC) along its concentration gradient into the cell (Figure 1). In the CD Na^+ enters the cytosol via the apical amiloride-sensitive epithelial Na^+ channel (ENaC) (Figure 2). On the basolateral side of these cells Na^+ is extruded by the Na^+/K^+ -ATPase. The Na^+ absorption from the luminal side is not only crucial to maintain Na^+ and fluid absorption but also to maintain the lumen-negative transmembrane potential which affects the activity of other ion channels and provides the driving force for potassium (K^+) and hydrogen (H^+) secretion (48). This is how excess Na^+ absorption in the DCT and CD contribute to hypokalemia and metabolic alkalosis.

Different mechanisms regulate Na^+ absorption in the distal nephron. Aldosterone binds to the mineralocorticoid receptor (MR), which then enhances Na^+ absorption via NCC and ENaC (Figure 2) (53). Stimulation of the MR activates genomic and non-genomic signaling pathways including the serum- and glucocorticoid-inducible protein kinase 1 (SGK1) to enhance Na^+ absorption in the distal nephron (Figure 2) (54). However, the MR cannot distinguish between aldosterone and cortisol. The cytoplasmic enzyme 11 β -hydroxysteroid dehydrogenase type 2 enzyme (11 β -HSD2) converts cortisol to inactive metabolites and thus prevents the MR from cortisol oversaturation (Figure 2). This is significant as cortisol is highly abundant, whereas aldosterone is much less present. The aldosterone to cortisol ratio in circulation is approximately 1:100 to 1:1,000 while the MR has a similar binding affinity for aldosterone and cortisol (55). Other modifiers for distal Na^+ and K^+ transport are two “with no lysine (K) serine/threonine protein kinases” (WNKs) called WNK-1

and WNK-4 which are mutated in pseudohypoaldosteronism type II (PHAII), a form of hyporeninemic hypertension (Figure 1) (56–58). WNK-1 and WNK-4 indirectly modify NCC activity by stimulating STE-20 serine proline alanine-rich kinase (SPAK) and oxidative stress response 1 kinase (OSR1) which in turn stimulates NCC phosphorylation (Figure 1) (59–62). WNK-1 also stimulates ENaC via SGK1 (not shown in Figure 2) (63). WNK-1 and WNK-4 mutations are thought to increase *WNK-1* and *WNK-4* gene expression, their activities on Na⁺ absorption and thereby cause volume overload (59,64). The identification of mutations in the genes for *Cullin 3 (CUL3)* and *Kelch-like 3 (KLHL3)* in patients with PHAII provided further insight in the regulation of WNKs (65). CUL3 and KLHL3 form a RING-type ubiquitin ligase complex, which promotes proteasomal degradation of WNKs (Figure 1) (66). Patients with *CUL3* and *KLHL3* mutations fail to degrade WNKs resulting in higher WNK activity and Na⁺ absorption (67,68). PHAII patients with *CUL3* and *KLHL3* mutations have a more severe phenotype than patients with *WNK-1* and *WNK-4* mutations (65). The regulation of Na⁺ transport remains a topic of investigation. Below we only discuss genes known to contribute to upregulated Na⁺ transport and hypertension. We will divide the diseases into disorders of the distal nephron (with mostly low aldosterone) and primary adrenal diseases (mostly high aldosterone) (Figure 3).

Distal nephron disorders (hyporeninemic-low aldosterone hypertension)

Liddle syndrome: This is an autosomal dominant disorder caused by the increased activity of ENaC in the principal cells located in the distal nephrons (69). This condition was first described by Grant Liddle in 1963 in a family with multiple members developing severe hypertension and hypokalemia (70). Liddle coined the term pseudoaldosteronism because the clinical presentation resembled hyperaldosteronism, but aldosterone levels were suppressed (70). ENaC is an obligate heterotrimer consisting of an α , β , and γ subunit. In the kidney, ENaC is primarily expressed in the apical membranes of the late DCT, connecting tubule, and CD. Under physiologic conditions, ENaC is regulated by aldosterone which upregulates the expression of ENaC channel via the MR in principle cells (Figure 2) (71). Patients with Liddle syndrome have mutations in the genes encoding the β or γ subunits of ENaC (72,73). Both subunits facilitate the binding of Nedd4, a factor that promotes ENaC internalization and degradation. The lack of Nedd4 binding may impair ENaC retrieval and increases the number of functional ENaC channels at the apical surface of principal cells (74,75). Subsequently, this leads to increased Na⁺ absorption, plasma volume expansion and hypertension (76). Additional studies also showed that truncation of the ENaC β subunit resulted in increased cell surface channel expression and channel open probability (77). Other mechanisms how certain ENaC mutations cause channel overactivity include insensitivity of ENaC to high intracellular Na⁺ concentration, changes of ENaC by proteolytic cleavage, channel open probability, and non-NEDD 4–2 mediated modifications of channel trafficking (75,78–81).

Liddle syndrome is considered the most common type of monogenic hypertension (48). Hypertension often starts in childhood but may be asymptomatic and remains undiagnosed. Laboratory studies show low plasma renin activity and aldosterone along with hypokalemia and metabolic alkalosis. Hypokalemia and metabolic alkalosis develop in response to increased Na⁺ reabsorption which creates a negatively charged lumen which promotes

secretion of K^+ and H^+ ions into the lumen (82). Treatment for Liddle syndrome consists of a low salt diet and inhibition of ENaC (83). Amiloride or triamterene directly interfere with ENaC, lower effectively blood pressure, and correct the hypokalemia and alkalosis in Liddle Syndrome. Both agents block the constitutively active ENaC and thus prevent excessive Na^+ reabsorption (84). Untreated Liddle syndrome patients are at grave risk for cardiovascular morbidity and mortality including strokes (84).

Gordon's syndrome (PHAII): This condition is also known as PHAII and caused by increased activity of NCC in the distal nephron (85). This condition was first characterized by Richard Gordon in several Australian families in 1970 (86). Because PHAII patients responded well to low-dose thiazide therapy, this condition has been associated with abnormal Na^+ absorption and enhanced NCC function long before the causative genes were identified (87). Although, it was well known that patients with Gordon syndrome have increased Na^+ reabsorption in the DCT, the molecular mechanism of increased NCC activity was only discovered over the last twenty years by Richard Lifton's group (56,65). His group identified autosomal dominant mutations, which increased the activity of WNK-1 and WNK-4 (Figure 1) (56,65). Both kinases increase the activity of NCC and increase the internalization of the renal outer medullary potassium (ROMK) channel which secretes K^+ , which contributes to hyperkalemia (88,89). Moreover, there are different characteristics attributed to a shorter kidney-specific and a more ubiquitous, longer version of WNK-1 (90). Large deletions within the first intron of the *WNK-1* gene result in increased WNK-1 expression. Missense mutations in *WNK-4* interfere with endosomal degradation of WNK-4. Both kinases phosphorylate SPAK/OSR, which in turn phosphorylates NCC resulting in increased NCC activity (Figure 1). Moreover, WNK-1 also stimulates ENaC via SGK1 (63). Other genes causing Gordon syndrome or PHAII include *KLHL3* and *CUL3* (65). Both proteins are part of a ubiquitin-protein ligase complex, which degrades WNKs (56,59,65). The presentation of patients with Gordon Syndrome/PHAII is quite variable. The patients are characterized by short stature, hypertension, hyperkalemia, muscle weakness, dental abnormalities, and intellectual developmental delay (56,65,91). The hyperkalemia and metabolic acidosis frequently precede the presentation of hypertension, and hypertension may only be diagnosed later in adult life (92,93). The initial presentation can sometimes be reminiscent of renal tubular acidosis (RTA) type 4 but in contrast to many forms of RTA type 4 glomerular filtration rate is usually normal in PHAII/Gordon syndrome (92). Patients with *CUL3* and *KLHL3* mutations usually have a more serious phenotype compared to patients with *WNK-1* and *WNK-4* mutations (65). Laboratory studies show suppressed plasma renin activity and normal or elevated aldosterone along with hyperkalemia and metabolic acidosis. The elevated aldosterone level may be due to direct activation of aldosterone due to hyperkalemia. The hyperkalemia seems to be due to a combination of increased ROMK internalization with less K^+ secretion and due to decreased Na^+ delivery to distal nephron (85,94). Interestingly, many PHAII/Gordon syndrome patients also display hypercalciuria. Treatment for these patients includes thiazides along with Na^+ and K^+ restriction (87).

Apparent mineralocorticoid excess (AME): This is a rare autosomal recessive disorder characterized by inactivating mutations of the *HSD11B2* gene, which encodes the 11β -HSD2 enzyme (95). This condition was first reported by Werder *et al.* in 1974 (96). The

11 β -HSD2 enzyme converts cortisol to cortisone. As outlined above this conversion is critical to prevent overstimulation of the MR by cortisol because cortisone has 100-fold less binding affinity to MRs. The mutation interferes with the proper conversion of cortisol to cortisone and results in higher cortisol levels, which then bind to the MR and result in overstimulation of Na⁺ absorption in the distal nephron (97). Characteristics of AME are unregulated activation of Na⁺ reabsorption, K⁺ secretion, and H⁺ secretion. These patients commonly develop end-organ damage in the heart, the central nervous system, the kidneys, and the retina, and the mortality in undiagnosed patients is considered to be high (98,99). Initially, it was thought, that this condition always presents in childhood with a grave phenotype including failure to thrive, low weight birth, and hypokalemic metabolic alkalosis. Later, milder phenotypes have been published with development of hypertension in adulthood and without any electrolyte abnormalities (100–102). These milder cases are due to only partial inactivation of 11 β -HSD2 (101,102). Patients can also present with a urinary concentration defect most likely caused by the chronic hypokalemia, which contributes to diabetes insipidus. Sometimes also hypercalciuria and nephrocalcinosis can be seen which are unclear in their etiology (101). AME should be considered in any patient with hyporeninemic, low aldosterone hypertension and indications of mineralocorticoid excess. The lack of 11 β -HSD2 activity can be detected in the urine with an abnormal ratio of cortisol metabolites [for example tetrahydrocortisol (THF)] and allotetrahydrocortisol (5 α -THF) to cortisone metabolites such as tetrahydrocortisone (THE) (103). A urine steroid profile showing the ratio of THF + 5 α -THF to THE in a 24 h urine can be diagnostic. In patients with a milder clinical course of AME the urine steroid profile can be normal requiring genetic testing. Treatment includes dietary Na⁺ restriction, use of MR antagonists (e.g., spironolactone and the more specific MR antagonist eplerenone), and K⁺ supplementation. Addition of amiloride may help to conserve K⁺. In case of hypercalciuria or nephrocalcinosis thiazides have been used. It is important to distinguish this condition from acquired suppression of 11 β -HSD2 activity by liquorice (104).

Hypertension exacerbated by pregnancy (Geller syndrome): The name of this condition is misleading because this disease is not limited to females (105). Affected patients have an autosomal dominant, activating mutation in the gene *NR3C2*, which encodes the MR. The activating mutation results in a constitutively active MR and overstimulation of Na⁺ absorption not only by aldosterone but also cortisone, and progesterone (105). While hypertension is present and possibly severe in nonpregnant patients, the hypertension is worsening during pregnancy. This condition can manifest at an early age and is accompanied by symptoms of mineralocorticoid excess. It is thought that the mutation increases the sensitivity of the MR to non-mineralocorticoid steroids, for example progesterone, which increases about 100-fold during pregnancy. Interestingly, the mutated form of the MR can also be stimulated by spironolactone. Laboratory studies show low renin, and aldosterone, and normal or low K⁺. Treatment includes salt restriction, thiazides, or ENaC antagonists. MR antagonists should be avoided.

Distal nephron disorders (hyporeninemic-low aldosterone hypertension—
Under physiologic conditions, aldosterone synthesis is regulated by calcium influx through voltage-gated Ca²⁺ channels (Ca_v1.3) located at the apical surface of adrenal granulosa cells

(Figure 4A) (106). At baseline, granulosa cells are hyperpolarized due to a high resting K^+ conductance with K^+ leaving the cells via inward rectifier potassium channel (Kir3.4). Inhibition of Kir3.4 either by binding of Ang II to angiotensin II receptors and/or by high serum potassium results in membrane depolarization (Figure 4B). This opens voltage-gated Ca^{2+} channels and results in Ca^{2+} influx which stimulates aldosterone synthase expression (106). Excessive aldosterone production can be primary due to bilateral adrenal hyperplasia or a unilateral adrenal adenoma (22,107). Even serum aldosterone levels within the reference range are capable of affecting blood pressure adversely (108). The aldosterone-to-renin ratio is a good indicator of aldosterone excess and is associated with hypertension, even in patients with normal aldosterone (22). Aldosterone and the RAAS may be rapidly stimulated due to hypotension and hypovolemia, which is mediated through adrenal aldosterone synthesis, intermediate-term activation may interfere with salt homeostasis, and long-term activation which results in structural changes of end-organs.

Primary aldosteronism (PA): This condition is commonly due to either an aldosterone-producing adrenal adenoma or bilateral adrenal hyperplasia and is one of the most common causes of secondary hypertension (109). Compared with patients affected by essential hypertension, patients with PA have an increased risk of cardiovascular disease (110,111). A higher risk for myocardial infarction, atrial fibrillation, kidney disease, and stroke has been persistently published in PA patients (111–114). PA is diagnosed in about 5% of hypertensive patients in a primary care setting. However, with increasing severity of hypertension this prevalence increases up to 20% (115,116). One report estimates that PA affects 8% and 13% of individuals with hypertension grades 2 and 3, respectively (117). Sporadic forms of hyperaldosteronism are common, familial forms are much less frequent with approximately 6% (118). The recommended screening test for both familial and non-familial forms of primary hyperaldosteronism is the ratio of plasma aldosterone concentration to plasma renin activity. A ratio higher than 30 is widely accepted as a positive screening-test result. However, normative values for the aldosterone-to-renin ratio are not well established for the pediatric population (119). The degree of aldosterone secretion and the aldosterone-to-renin ratio correlate with severity of hypertension (117). Confirmation of the diagnosis is dependent upon measurement of urinary aldosterone in a 24 h urine collection and an aldosterone suppression test applying oral Na^+ , IV saline, fludrocortisone, or captopril. The gold standard to diagnose PA is adrenal venous sampling which is mostly performed in adults (120). In patients with a family history of hypertension who present with hypertension and hypokalemia, one should consider screening for genetic causes of primary hyperaldosteronism. Next, we will outline a number of genetically inherited forms of hyperaldosteronism.

Familial hyperaldosteronism (FH): This group includes a number of autosomal dominant, rare conditions. They usually present with early-onset hypertension, hypokalemia, metabolic alkalosis, and high aldosterone-to-renin ratio (15). Four different types of FH are known, and it can be challenging to distinguish them from sporadic PA based on clinical findings and biochemical tests (109).

Familial hyperaldosteronism type I (FH-1 or glucocorticoid-remediable

aldosteronism): FH-I—also known as GRA—was first described in 1966 by Sutherland *et al.* and is responsible for <1% of all PA patients (121,122). FH-I/GRA is an autosomal dominant condition and was the first form of monogenic hypertension to be recognized as a single-gene hypertensive disorder (123). Aldosterone is synthesized by aldosterone synthase in the zona glomerulosa of the adrenal cortex under the control of angiotensin II. Cortisol is produced by 11 β -hydroxylase in the zona fasciculata under the control of the adrenocorticotrophic hormone (ACTH). The genes encoding aldosterone synthase and 11 β -hydroxylase are located adjacent to each other on chromosome 8. Lifton *et al.* identified that FH-1/GRA is due to a hybrid/chimeric gene on chromosome 8q consisting of the regulatory region of the 11 β -hydroxylase gene, *CYP11B1*, coupled with the structural region of the aldosterone synthase gene, *CYP11B2*, caused by asymmetrical cross-over (123). This means that the hybrid gene contains an ACTH-responsive promoter and an aldosterone synthase encoding region which results in ACTH-dependent stimulation and is independent of renin, angiotensin, K⁺ or Na⁺ balance (Figure 4C) (123–125). Patients with this condition present with hypertension in infancy or childhood and are characterized by profound cardiovascular morbidity and an increased risk for thoracoabdominal aneurysms and hemorrhagic strokes due to ruptured aneurysms (126–129). Therefore, all patients with genetically proven FH-I/GRA should undergo screening with cerebral MR angiogram at puberty, and subsequently every 5 years (107,130). However, also milder forms and even normotensive patients with GRA have been published (126,131,132). Some patients were only diagnosed in adolescence (133). Hypokalemia is only present in about 50% of GRA patients and some also display mild metabolic alkalosis (126,131,133). The pattern of crossovers are different in each pedigree suggesting that the mutations occurred independently of each other in each kindred (131). GRA seems to be much less prevalent in African-Americans. Plasma renin activity is typically suppressed while aldosterone levels can be increased (aldosterone-to-renin ratio >30, normal is <20). In some patients the aldosterone may be normal and only the aldosterone-to-renin ratio may be elevated. Other diagnostic tools include a dexamethasone suppression test, urinary steroid profile (with an elevated 18-oxocortisol level), adrenal imaging, and adrenal vein sampling. Improved genetic testing capabilities have eliminated the need for challenging studies and sampling. Preferred treatment of GRA consists of low-dose glucocorticoids to downregulate ACTH-stimulated mineralocorticoid production, amiloride, and spironolactone, which blocks binding of aldosterone to the MR. To treat hypertension due to GRA the steroid dose is usually not very high dose. Thiazide diuretics are not the recommended first-line treatment, but might improve control of blood pressure when used concurrently with spironolactone. Thiazide diuretics can cause marked hypokalemia secondary to increased Na⁺ delivery to the cortical collecting duct.

Familial hyperaldosteronism type II (FH-II): Initially described by Stowasser *et al.* in 1992, 13 patients from five families were found to have PA, which was not suppressed by a dexamethasone challenge (distinguishing it from FH-I/GRA). FH-II is now recognized as another autosomal dominant cause of secondary hypertension (134). A genetic locus for FH-II has been described on chromosome 7p22 (135). Dominant gain-of-function mutations of the *CLCN2* gene were identified (136,137). FH-II has a prevalence between 1.2% and 6% in adults with PA (109). This gene encodes the voltage-gated chloride

channel CIC-2 in the adrenal zona glomerulosa. Mutations result in a lower threshold for membrane depolarization in the adrenal zona glomerulosa and allow for stimulation of voltage-gated calcium channels. Consequently, the higher calcium influx upregulates *CYP11B2* expression, which encodes aldosterone synthase (Figure 4D) (136). A mouse model for FH-II with one of the most common human missense mutations in *CLCN2* reproduced the human phenotype and confirmed the role of CIC-2 in aldosterone synthesis (138). Patients with FH-II are clinically indistinguishable from those with sporadic forms of PA due to bilateral adrenal hyperplasia. FH-II patients frequently have a family history of adrenal hyperplasia or adenoma. Given extended inclusion criteria FH-II seems to be more common than previously considered and may be the most common cause of inherited hypertension in adults (139). In contrast to FH-I/GRA, FH-II patients usually present in adolescence and in adulthood while irregularities of the RAAS may be detected earlier (140). FH-II patients can also develop aldosterone-producing adenoma or bilateral adrenal hyperplasia. It is important to differentiate between FH-I and FH-II as they require different treatments. Direct genetic testing for the presence of the chimeric gene in FH-I/GRA is available and has been shown to have 100% sensitivity and specificity for diagnosing FH-I/GRA (141). FH-I/GRA patients are treated with glucocorticoids to decrease ACTH driven overproduction of aldosterone. By contrast, hypertension in FH-II is unresponsive to glucocorticoids, but MR antagonists and adrenalectomy are effective.

Familial hyperaldosteronism type III (FH-III): This is another autosomal dominant rare form of monogenic hypertension accounting for approximately 0.3% of PA patients (142,143). The causative gene for FH-III is *KCNJ5* which encodes the inwardly rectifying K⁺ channel Kir3.4, also named GIRK4 (144). *KCNJ5* mutations cause both familial and sporadic forms of primary hyperaldosteronism (144,145). *KCNJ5* somatic mutations in the adrenal gland are also responsible for 40% of aldosterone producing adenomas (144,146). As a consequence of the *KCNJ5* mutation the selectivity of the Kir3.4 pore is lost and a higher influx of Na⁺ occurs through Kir3.4 (Figure 4E). This results in membrane depolarization, calcium influx and increased *CYP11B2* expression, encoding for aldosterone synthase (147). Patients can present with bilateral adrenal hyperplasia, severe hypertension, and hypokalemia. While most patients with FH-III are adults, a few pediatric patients with FH-III are also published (145,148–151). Genetic testing is very helpful to make the correct diagnosis. There should be a low threshold for adrenal computed tomography and adrenal venous sampling. Follow-up may include repeated imaging of the adrenal glands to exclude development of a mass that requires surgical resection. Some mutations are not germline mutations but only somatic *KCNJ5* mutations, and will only be detected in tissue from the adrenal gland (144).

Familial hyperaldosteronism type IV (FH-IV): This type of familial hyperaldosteronism is caused by autosomal dominant germline mutations in *CACNA1H*. This gene encodes for the α subunit of the calcium channel Cav3.2 which is highly abundant in the zona glomerulosa of the adrenal gland (Figure 4F) (152). Gain-of-function mutations in *CACNA1H* increase calcium influx and increased aldosterone production (153). The symptoms are comparable to other forms of FH. Genetic testing is recommended for patients younger than 10 years of age with PA and hypertension (154). Specific treatment is not

available for patients with this condition but mineralocorticoid antagonists or adrenalectomy improve hypertension (152).

Other genetic forms of FH also include either somatic and/or germline mutations in *CACNA1D*, *ATP1A1*, *ATP2B3*, and *PRKACA* causing PA and aldosterone-producing adenomas (155–158).

Congenital adrenal hyperplasia: The term ‘congenital adrenal hyperplasia’ (CAH) describes a group of syndromes caused by defects in cortisol biosynthesis. CAH is inherited in an autosomal recessive fashion. CAH is caused by a variety of different enzymatic defects. When 21-hydroxylase (*CYP21A2*) is deficient—the most common cause of CAH—patients are usually not hypertensive. In 11 β -hydroxylase (*CYP11B1*) and 17 α -hydroxylase (*CYP17*) deficiencies, patients present with hypertension and hypokalemia due to the overproduction of ACTH, 21-hydroxylated mineralocorticoids, including deoxycorticosterone (DOC), which has mineralocorticoid activity and stimulates the MR (159,160). The patients develop hypertension due to Na⁺ retention mediated by the distal nephron. Moreover, defects in *CYP11B1* and *CYP17* inhibit cortisol synthesis with a subsequent reduction in feedback inhibition of ACTH secretion. Consequently, the increased ACTH secretion stimulates production of steroid precursors proximal to the ‘blocked’ enzymatic step, leading to excessive levels of DOC. In both disorders, patients present with hypertension and hypokalemia early in life. Signs of androgen excess distinguish the two disorders; 11 β -hydroxylase deficiency causes virilization in girls and precocious puberty in boys, whereas 17 α -hydroxylase deficiency results in sex hormone deficiency, primary amenorrhea and delayed sexual development in girls, and ambiguous genitalia in boys. The correct diagnosis is made by the clinical presentation and plasma or urine steroid profiles. Genetic diagnosis of both conditions relies on testing for mutations that either severely depress or abolish enzyme activity. The hypertension can be addressed with MR antagonists. Both conditions are treated with exogenous glucocorticoids, which normalize ACTH secretion and ACTH-mediated build-up of cortisol precursors proximal to the enzymatic deficiency, including DOC. Acquired forms of CAH caused by DOC-producing tumors typically present later in life.

Familial glucocorticoid resistance: Individuals with mutations in the glucocorticoid receptor (GR) do not respond to cortisol and lack the subsequent suppression of cortisol synthesis. Due to the GR unresponsiveness affected patients develop overproduction of cortisol and androgens (161). The elevated cortisol levels then overwhelm the capability of the 11 β -HSD2 to convert it to cortisone. This results in MR activation and excessive Na⁺ absorption. Given the GR resistance to cortisol patients do not develop cushingoid symptoms. The inheritance depends on the specific mutation and the degree of symptoms and hypertension depend on the severity of GR impairment (162). Complete GR inactivation is incompatible with life. The diagnosis is made with significantly elevated plasma cortisol levels. The hypertension is treated with MR antagonists.

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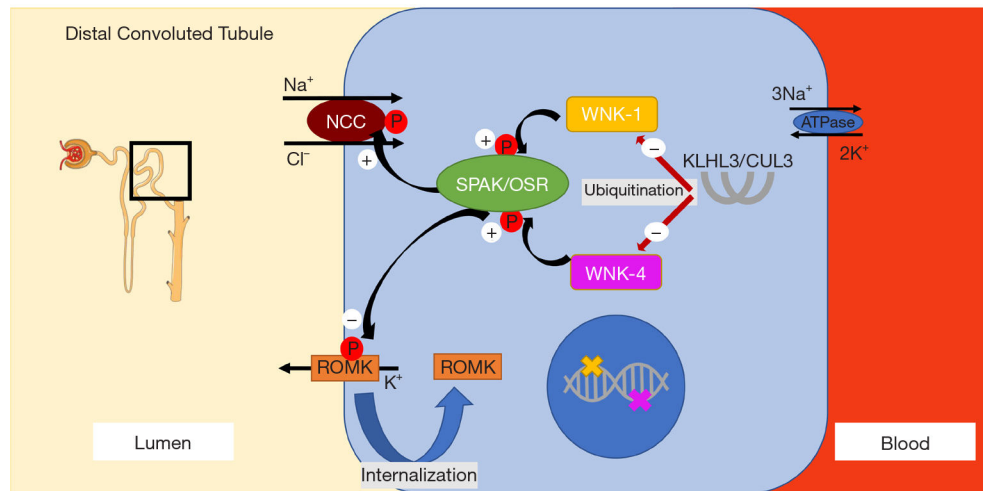


Figure 1.

Sodium reabsorption and potassium secretion at the level of the distal convoluted tubule. In the DCT WNK-1 and WNK-4 increase the activity of NCC which reabsorbs Na⁺ and increase the internalization of ROMK channel which secretes K⁺. Both kinases phosphorylate SPAK/OSR which in turn phosphorylates NCC and ROMK resulting in increased Na⁺ reabsorption by NCC and decreased ROMK availability at the apical surface, respectively. WNK-1 also stimulates ENaC via SGK1 (not shown) in the CD. In Gordon syndrome large deletions (yellow cross) within the first intron of the *WNK-1* gene result in increased WNK-1 expression. Missense mutations (purple cross) in *WNK-4* interfere with endosomal degradation of WNK-4. *KLHL3* and *CUL3* encode for proteins that are part of a ubiquitin-protein ligase complex that degrades WNKs. Inactivating mutations in these genes result in increased availability of WNK-1 and WNK-4. DCT, distal convoluted tubule; ENaC, amiloride sensitive-epithelial (Na⁺) channel; NCC, sodium chloride cotransporter; ROMK, renal outer medullary potassium (K⁺) channel; WNK, with no lysine serine/threonine protein kinases gene; *KLHL3*, Kelch-like 3 gene; *CUL3*, *Cullin 3* gene; SPAK, SPS1-related proline/alanine-rich kinase; OSR, oxidative stress-responsive kinase 1.

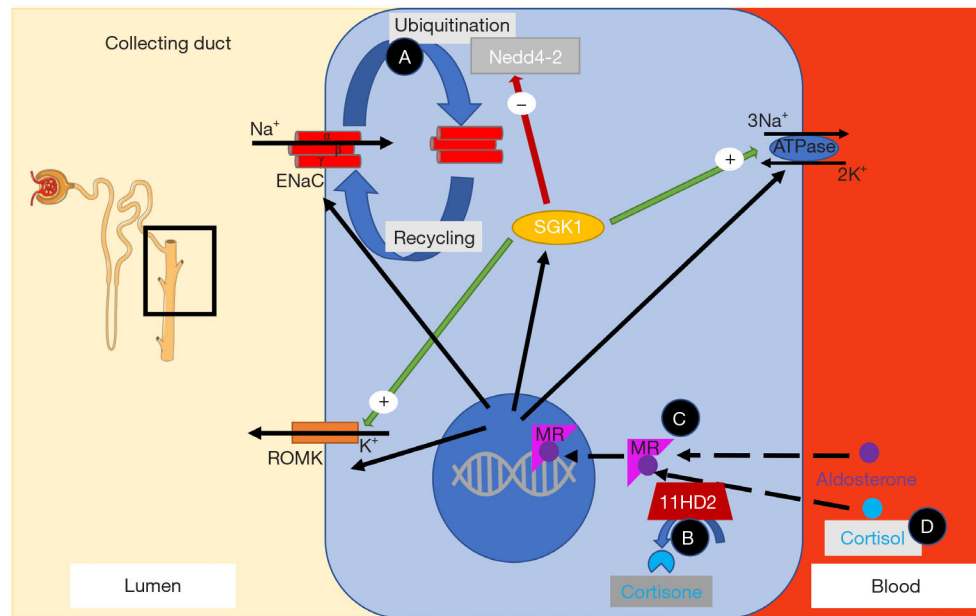


Figure 2.

Sodium reabsorption and potassium secretion at the level of the collecting duct. In the CD segment of the nephron, aldosterone binds to MR which activates genomic and non-genomic signaling pathways including SGK1 to enhance ENaC and Na^+ absorption. SGK1 enhances Na^+ reabsorption and K^+ secretion by increasing the activity of ENaC, ROMK, and Na^+/K^+ ATPase. SGK1 increases ENaC availability by decreasing Nedd4–2 mediated degradation of ENaC. In Liddle syndrome (A) there are mutations in the genes encoding the beta or gamma subunits of ENaC. These mutations prevent the binding of Nedd4, a factor that promotes ENaC internalization and degradation, and thus increases the number of functional ENaC at the apical surface of principal cells. The MR receptor binds aldosterone and cortisol. Although cortisol is more available, it is quickly converted to cortisone (inactive metabolite) by the 11β -HSD2 enzyme. This will prevent overstimulation of MR. In AME (B), there are inactivating mutations of the *HSD11B2* gene, which encodes the 11β -HSD2 enzyme. This will make cortisol more available as the conversion to cortisone is impaired, and will overstimulate MR. In hypertension exacerbated by pregnancy (Geller syndrome) (C), there are activating mutations in the gene *NR3C2*, which encodes the MR. This results in a constitutively active MR and overstimulation of Na^+ absorption not only by aldosterone but also cortisone, and progesterone. In familial glucocorticoid resistance (D), the levels of cortisol are elevated due to glucocorticoid receptor resistance. The elevated cortisol levels then overwhelm the capability of the 11β -HSD2 to convert it to cortisone. This results in MR activation and excessive Na^+ absorption. CD, collecting duct; MR, mineralocorticoid receptor; SGK1, Serum/Glucocorticoid Regulated Kinase 1; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel; Nedd4–2, neural precursor cell expressed developmentally down-regulated 4–2 (ubiquitin protein ligase); AME, apparent mineralocorticoid excess; 11β -HSD2, 11 beta-hydroxysteroid dehydrogenase enzyme type 2; GR, glucocorticoid receptor.

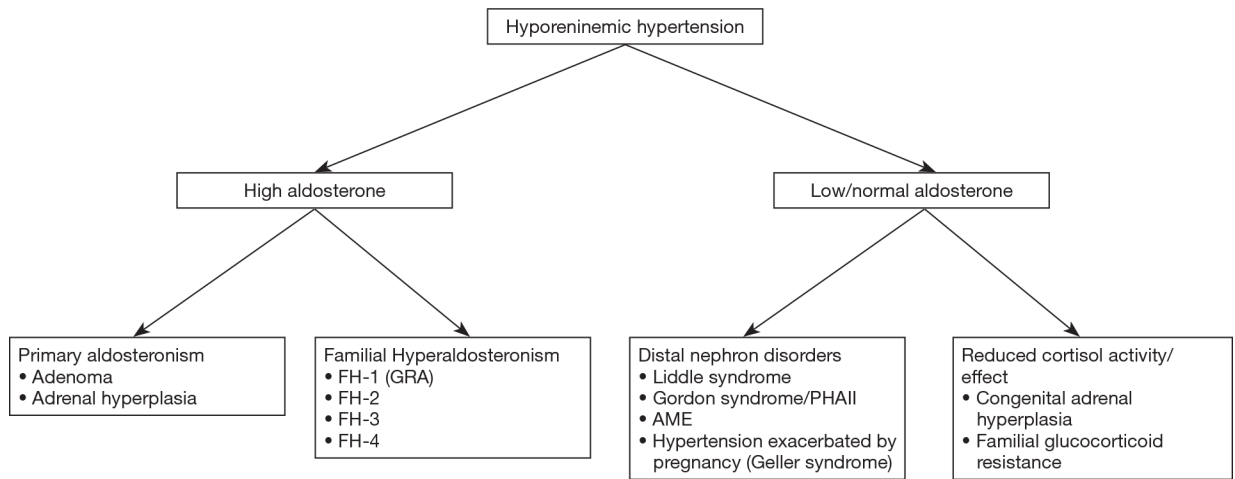


Figure 3.

Etiology of hyporeninemic hypertension based on aldosterone level. Hyporeninemic hypertension can be classified according to aldosterone level. Although Gordon syndrome is a distal nephron disorder, aldosterone level is variable (normal to high). GRA, glucocorticoid-remediable aldosteronism; PHAII, pseudohypoaldosteronism type II; AME, apparent mineralocorticoid excess.

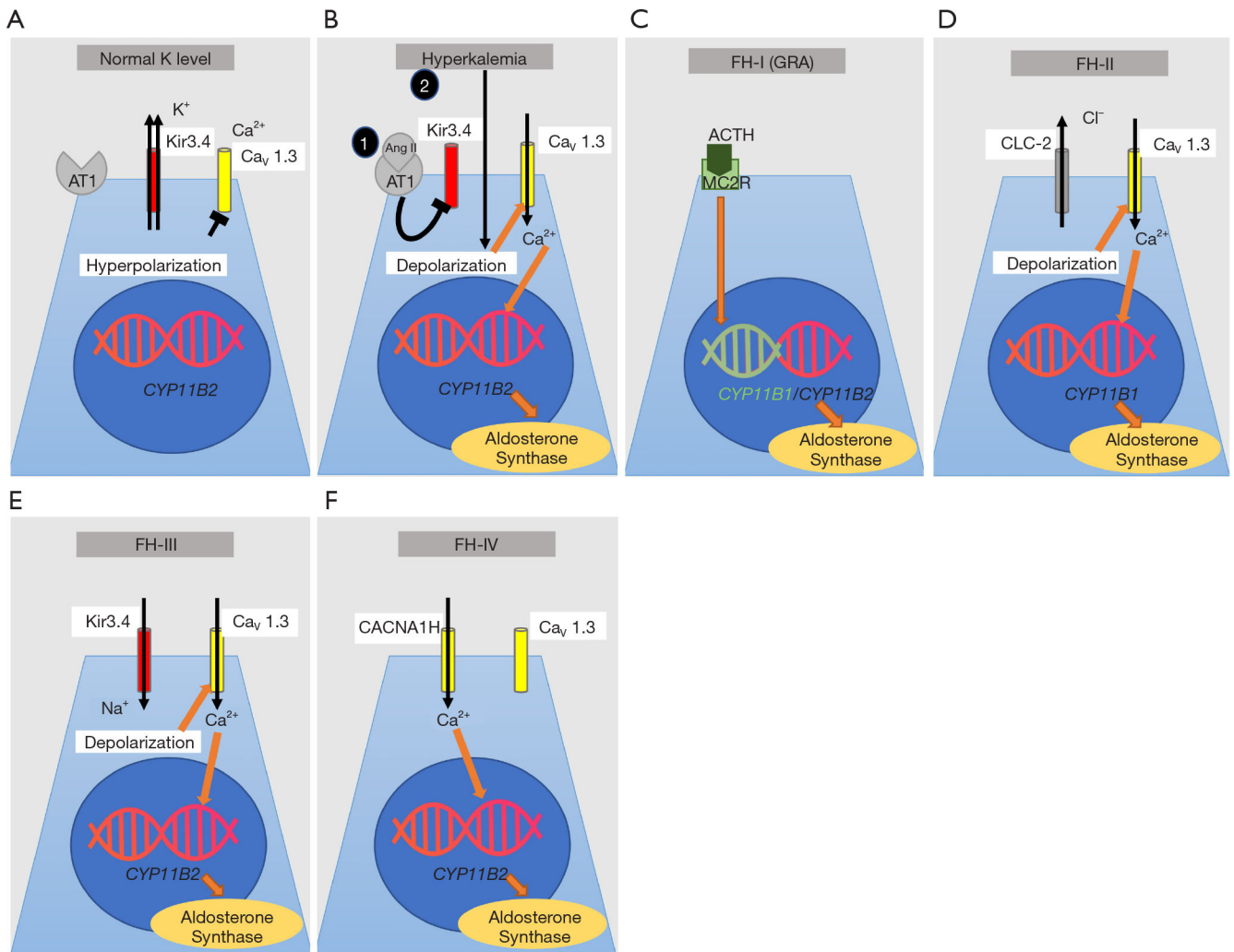


Figure 4.

Physiologic regulation and mechanisms of dysregulation of aldosterone synthesis in hyperaldosteronism. Under physiological conditions, aldosterone synthesis is regulated by calcium influx via voltage-gated Ca^{2+} channels ($\text{Ca}_v1.3$) located at the apical surface of via Kir3.4. (B) Binding of Ang II to angiotensin II type 1 receptors ① and/or hyperkalemia ② inhibit Kir3.4 and result in depolarization of the membrane potential. This causes Ca^{2+} influx through voltage-gated Ca^{2+} channels, which increases intracellular Ca^{2+} levels, and thereby stimulates aldosterone synthase expression. (C) In FH-I (GRA), a fusion between the promoter sequence of *CYP11B1* (11 β -hydroxylase) with the exons of *CYP11B2* (aldosterone synthase gene) creates a hybrid/chimeric gene with ACTH-responsive promoter (green) and aldosterone synthase (red) encoding region. This results in ACTH-dependent aldosterone synthase expression that is independent of renin-angiotensin axis or K^+ serum level. (D) In FH-II, mutations of the *CLCN2* gene, encoding the voltage-gated chloride channel CLC-2, result in a lower threshold for membrane depolarization in the adrenal zona glomerulosa and stimulation of voltage-gated calcium channels which will ultimately increase the expression of aldosterone synthase. Similar effect is seen in FH-III. (E) In FH-III *KCNJ5* mutations result in altered ion selectivity of Kir3.4 (K^+ channel). This results

in Na⁺ influx into the cell and depolarization rather than K⁺ efflux and hyperpolarization. (F) In FH-IV, a gain of function mutation in *CACNA1H* encoding Ca_v3.2 calcium channel result in increased Ca²⁺ influx and subsequent aldosterone synthase expression. AT1, angiotensin I receptor; Ang II, angiotensin II; Kir3.4, potassium channel inwardly rectifying; *KCNJ5*, Kir3.4 gene; Ca_v1.3, calcium channel voltage dependent; *CACNA1H*, Ca_v1.3 gene; *CYP11B2*, aldosterone synthase gene; *CYP11B1*, 11β-hydroxylase gene; ACTH, adrenocorticotrophic hormone; MC2R, melanocortin receptor 2; CIC-2, voltage-gated chloride channel; *CLCN2*, CIC-2 gene.

Table 1

Causes of secondary hypertension

Age	Primary or secondary	Causes for secondary hypertension
Birth to 1 year	Secondary (99%)	Neonatal: Maternal hypertension, maternal substance abuse, antenatal steroids, maternal obesity, and maternal diabetes mellitus, low birthweight, hypoxia, prematurity Medications: steroids, indomethacin, vasopressors, bronchodilators, theophylline, caffeine, vitamin D intoxication, pancuronium, erythropoietin Neurologic: seizures, increased intracranial pressure, intracranial hemorrhage, pain Renal: renal parenchymal disease, congenital nephrotic syndrome, ARPKD, renovascular defect, cortical necrosis, pseudohypoadosteronism type II Pulmonary: bronchopulmonary dysplasia Endocrine: congenital adrenal hyperplasia, hyperthyroidism, hyperaldosteronism, adrenal hemorrhage Neoplasia: Wilms tumor, Neuroblastoma, mesoblastic nephroma Cardiac: coarctation of aorta, patent ductus arteriosus Medications: steroids, NSAIDs, vasopressors, bronchodilators, vitamin D intoxication, pancuronium, erythropoietin, herbal medications, decongestants, oral contraception, cyclosporine, tacrolimus, ADHD medications Neurologic: seizures, increased intracranial pressure, intracranial hemorrhage, pain Renal: acute kidney injury, tuberos sclerosis, multicystic-dysplastic kidneys, obstructive uropathy, reflux uropathy, renal hypoplasia, interstitial nephritis, pyelonephritis, cortical necrosis, hypercalcemia Renovascular disease: renal artery stenosis, renal venous thrombosis, mid-aortic syndrome, vascular compression Endocrine: hyperthyroidism, hyperaldosteronism, congenital adrenal hyperplasia Neoplasia: Wilms tumor, pheochromocytoma Cardiac: coarctation of aorta Same causes as in the 1–12 years group
Age 1–12 years	Secondary (70–85%); primary (15–30%)	NSAIDs, non-steroidal anti-inflammatory drugs; ADHD, attention deficit hyperactivity disorder.
Age 12–18 years	Primary (85–95%); secondary (5–15%)	

Table 2

Summary of the different causes of monogenetic hypertension

Monogenic HTN (low renin)	Aldosterone level	Genetic mutation	Mechanism	Inheritance	Electrolyte derangement	Management
Liddle syndrome	Low	<i>SCNN1B</i> , <i>SCNN1G</i>	Increased ENaC expression and activity Decreased ENaC degradation	AD	Hypokalemia; metabolic alkalosis	Amiloride; triamterene; sodium restriction
Gordon syndrome (PHAII)	Normal to high	<i>WNK-1</i> , <i>WNK-4</i> , <i>KLHL-3</i> , <i>CUL3</i>	Increased NCC activity Increased ROMK channel internalization	AD	Hyperkalemia, metabolic acidosis	Thiazide; sodium restriction; potassium restriction
Apparent mineralocorticoid excess (AME)	Low	<i>HSD11B2</i>	Inactivation of 11HD2 Increased cortisone binding to MR	AR	Hypokalemia; metabolic alkalosis	Spironolactone; eplerone; sodium restriction
Hypertension exacerbated by pregnancy (Geller syndrome)	Low	<i>NR3C2</i>	Activation of MR	AD	Hypokalemia; metabolic alkalosis	Thiazide; amiloride; sodium restriction; avoid MR antagonists
Glucocorticoid-remediable aldosteronism (FH-1)	High	<i>CYP11B1</i> / <i>CYP11B2</i> cross over	ACTH mediated- aldosterone production	AD	± Hypokalemia; ± metabolic alkalosis	Low dose steroid; amiloride; spironolactone
FH-2	High	<i>CLCN2</i>	Depolarization of granulosa cells	AD	± Hypokalemia; ± metabolic alkalosis	Adrenalectomy; amiloride; spironolactone
FH-3	High	<i>KCNJ5</i>	Depolarization of granulosa cells	AD	± Hypokalemia; ± metabolic alkalosis	Adrenalectomy; amiloride; spironolactone
FH-4	High	<i>CACNA1H</i>	Increased calcium influx in granulosa cells	AD	± Hypokalemia; ± metabolic alkalosis	Adrenalectomy; amiloride; spironolactone

ENaC, amiloride sensitive-epithelial (Na⁺) channel; NCC, sodium chloride cotransporter; PHAII, pseudohypoaldosteronism type II; ROMK, renal outer medullary potassium (K⁺) channel; W/NK, with no lysine serine/threonine protein kinases gene; *KLHL-3*, Kelch-like 3 gene; *CUL3*, Cullin 3 gene; *11HD2*, 11 β -hydroxysteroid dehydrogenase type 2 enzyme; FH, familial hyperaldosteronism; *CYP11B1*, 11- β - hydroxylase gene; *CYP11B2*, Aldosterone synthase gene; *CLCN2*, voltage gated chloride channel gene; *KCNJ5*, inward rectifying K⁺ channel gene.

Table 3

The search strategy summary

Items	Specification
Date of search	24th April, 2021
Databases and other sources searched	PubMed
Search terms used	Hyporeninemic hypertension, monogenic hypertension, genetic hypertension, low renin hypertension, inherited hypertension, Liddle syndrome, Gordon syndrome, Apparent Mineralocorticoid Excess, Geller syndrome, primary hyperaldosteronism, familial hyperaldosteronism, Glucocorticoid Remediabale Aldosteronism, congenital adrenal hyperplasia, familial glucocorticoid resistance
Timeframe	We did not apply a timeframe, but we focused on the last 5 years and pediatric cases; for pathophysiology we concentrated on the most recent publications
Inclusion and exclusion criteria	Inclusion criteria: publications in English language and focus on pediatric population
Selection process	Selection of references was agreed on by both authors
Any additional considerations, if applicable	Not applicable