JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/14269

Low renin forms of monogenic hypertension: review of the evidence

Ugochi Chinenye Okorafor[1], Uchechi Chioma Okorafor[2]

[1]Department of Cardiology, Meridian Cardiac Center, Festac Town, Lagos, Nigeria
[2]Department of Medicine and Surgery, College of Medicine, University of Ibadan, University Of Ibadan, Ibadan, Nigeria.

Received: 2024-01-04.
Accepted: 2024-02-05.

J Clin Med Kaz 2024; 21(1):14-20

Corresponding author:
UGOCHI CHINENYE OKORAFOR.
E-mail: ugochi.c.okorafor@gmail.com;
ORCID: 0009-0002-1928-0105.

Abstract

Background: Monogenic hypertension syndromes result from a single genetic mutation and present with severe, refractory hypertension, distinct laboratory abnormalities, and a positive family history. These syndromes are often unrecognized or misdiagnosed as essential hypertension, thus preventing proper treatment. The rise of molecular genetics has brought these conditions to the limelight, and physicians must be kept abreast of the latest in this field. This paper aims to educate doctors to recognize and institute appropriate management early to prevent end-organ damage.

Discussion: These syndromes all affect sodium transport in the distal nephron of the kidneys. However, they are divided based on the location of the primary disorder, i.e., the adrenal glands or the distal nephron and discussed in that manner. Tables provide an overview of the different syndromes and provide essential information in a snapshot.

Conclusion: The widespread availability of genetic testing facilities will aid in the earlier diagnosis of these conditions to prevent morbidity.

Keywords: Apparent Mineralocorticoid Excess; Congenital Adrenal Hyperplasia; Familial Hyperaldosteronism; Gordon Syndrome; Hypertension; Liddle Syndrome.

Introduction

Hypertension is a significant risk factor in the development of cardiovascular diseases (CVD) [1] and is also a major contributor to the global burden of disease [2]. Defined as systolic blood pressure (SBP) of 140mmHg or more and/or diastolic blood pressure (DBP) of 90mmHg or more [3], it is responsible for one in eight deaths globally [4]. Monogenic hypertension syndromes have distinct causative genetic mutations with identifying clinical and/or laboratory characteristics [5, 6]. They are subserved by abnormally high sodium transport in the distal nephron [7–9]. Of particular note is their presentation in childhood with severe, refractory hypertension, propensity to develop end-organ failure and associated family history [10]. This paper discusses low renin monogenic hypertension disorders. They are grouped as adrenal gland and distal nephron disorders based on their pathophysiology. We aim to educate physicians on best management practices. Table 1 provides an overview of these syndromes and their management.

Methods

Searches were conducted in Google Scholar and PubMed. Search terms included “monogenic hypertension”, “low renin hypertension”, “familial hyperaldosteronism”, “congenital adrenal hyperplasia”, “secondary hypertension”, “Liddle syndrome”, “Gordon syndrome”, “Geller syndrome”, “apparent mineralocorticoid excess”, and “familial glucocorticoid resistance”.

Inclusion criteria

1. Articles included in the review had to be written in English.
2. Articles had to have been released between September 2018 and August 2023.

Exclusion criteria

1. Publications noted to not have passed through the peer review process.
2. Articles not published in English.
3. Publications released before September 2018 and after August 2023.

Eighty-two articles and books were retrieved and reviewed, after which 56 were selected for discussion.

Table 1 Overview of low-renin monogenic hypertension syndromes

Syndrome	Gene locus	Affected gene	Gene product	Mode of Inheritance	Pathophysiology	Management
Familial Hyperaldosteronism-1	8q24.3	CYP11B1/ CYP11B2 gene chimera	Aldosterone synthase	AD	GOF mutation in the chimeric gene allows aldosterone synthase to be responsive to ACTH stimulation	Glucocorticoids (dexamethasone or prednisolone), MR antagonists (spironolactone or eplerenone), ENaC blockers (amiloride or triamterene)
Familial Hyperaldosteronism-2	3q27.1	CLCN2	Voltage-gated chloride channel-2	AD	GOF mutation in the affected gene allows for the synthesis of an overly permeable chloride channel with cell membrane depolarisation and production of aldosterone synthase	MR antagonists, unilateral adrenalectomy
Familial Hyperaldosteronism-3	11q24.3	KCNJ5	GIRK4	AD	GOF mutation in the KCNJ5 leads to loss of selectivity in the gene product, GIRK4	MR antagonists, bilateral adrenalectomy
Familial Hyperaldosteronism-4	16p13.33	CACNA1H	α-subunit of CaV3.2 (T-type calcium channel)	AD	Intracellular calcium ion influx secondary to GOF mutation in the responsible gene with stimulation of aldosterone synthase synthesis	No specific treatment. MR antagonists can be used.
Congenital Adrenal Hyperplasia Type IV	8q24.3	CYP11B1	11β-hydroxylase	AR	Accumulation of DOC and deoxycortisol which both have mineralocorticoid effect	Glucocorticoids, MR antagonists, Calcium channel blockers
Congenital Adrenal Hyperplasia Type V	10q24.32	CYP17A1	17α-hydroxylase	AR	Increased production of DOC with excessive activity at the MR	MR antagonists
Familial Glucocorticoid Resistance	5q31-q32	NR3C1	Glucocorticoid receptor	AD,AR	LOF mutation in the affected gene encodes for a glucocorticoid receptor unresponsive to cortisol. Accumulation of cortisol (which has mineralocorticoid activity) causes excess MR activation	Dexamethasone
Liddle syndrome	16p12.2	SCNN1B	ENaC β-subunit	AD	Reduced degradation of ENaCs secondary to the mutations causes increased sodium and water reabsorption	ENaC blockers, dietary sodium restriction
	16p12.2	SCNN1G	ENaC γ-subunit	AD		
	12p13.31	SCNN1A	ENaC α-subunit	AD		
Geller syndrome	4q31.23	NR3C2	Mineralocorticoid receptor	AD	GOF mutation in the MR makes it sensitive to progesterone, a natural antagonist	ENaC blockers, finerenone, dietary sodium restriction
Apparent Mineralocorticoid Excess	16q22.1	HSD11B2	11β-hydroxysteroid dehydrogenase type II	AR	Defects in the metabolism of cortisol cause its accumulation and excess activity at the MR	MR antagonists, dietary sodium restriction, ENaC blockers, Calcium channel blockers
Gordon syndrome	1q31-q42	Not known	Not known	AD	All mutations known to Gordon syndrome work to upregulate the NCC in the distal nephron resulting in increased sodium reabsorption and hypertension	Thiazide diuretics, dietary sodium and potassium restriction
	17q21.2	WNK-4	With-no-lysine kinase 4	AD		
	12p13.33	WNK-1	With-no-lysine kinase 1	AD		
	5q31.2	KLHL3	Kelch-like 3	AD,AR		
	2q36.2	CUL3	Cullin3	AD		

ACTH – Adrenocorticotropic Hormone, AD – Autosomal dominant, AR – Autosomal recessive, DOC – deoxycorticosterone, ENaC – Epithelial sodium channel, GOF – Gain of function, LOF – Loss of function, MR – Mineralocorticoid receptor, NCC – Sodium-chloride cosymporter.

Discussion

A. Disorders of the Adrenal Gland

- Familial Hyperaldosteronism Type 1 (FH-1)

First described in 1966 and also known as Glucocorticoid-remediable aldosteronism (GRA), FH-1 is an autosomal dominant condition resulting from a mutation on chromosome 8q24.3 [11, 12]. A chimeric gene resulting from the crossing over of genes typically near each other, namely CYP11B1 and CYP11B2 (which encode 11β-hydroxylase and aldosterone synthase, respectively), is produced during DNA replication in individuals with this condition [12]. This mutant gene was identified by Lifton and colleagues in 1992 and encodes for aldosterone synthase that is responsive to adrenocorticotropic hormone (ACTH) stimulation [13, 14]. Aldosterone is now produced in the zona glomerulosa and alongside cortisol in the zona fasciculata of the adrenal glands [15]. This leads to supraphysiologic aldosterone concentrations in the bloodstream, increased sodium and water reabsorption, mild hypokalemia,

Table 2 Overview of Familial Hyperaldosteronism

TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT	AD/AR	GOF/LOF	AGE AT ONSET
FH-1	8q24.3	CYP11B1/CYP11B2 chimeric gene	Aldosterone synthase	AD	GOF	Variable
FH-2	3q27.1	CLCN2	Voltage-gated chloride channel 2	AD	GOF	Variable
FH-3	11q24.3	KCNJ5	GIRK-4	AD	GOF	Infancy/early childhood
FH-4	16p13.3	CACNA1H	CaV3.2	AD	GOF	Variable

AD – Autosomal dominant, AR – Autosomal recessive, FH – Familial hyperaldosteronism, GOF – Gain of function, LOF – Loss of function

metabolic alkalosis, low plasma renin levels, and hypertension [16, 17].

These patients have been noted to have a higher risk of hemorrhagic strokes and, even when normotensive, have increased left ventricular wall thickness with diastolic dysfunction [18, 19]. Diagnosis is conclusive with genetic testing [20]. Additional laboratory investigations include plasma aldosterone and renin levels alongside testing for aldosterone suppression levels with dexamethasone [21]. Treatment involves glucocorticoid replacement (i.e., dexamethasone or prednisolone) at the lowest dose to allow for disease remission and also prevent Cushing syndrome [22]. Mineralocorticoid antagonists (i.e., spironolactone or eplerenone) and epithelial sodium channel (ENaC) blockers can serve as adjuncts for better blood pressure control [23].

- Familial Hyperaldosteronism Type 2 (FH-2)

FH-II is caused by mutations in the CLCN2 gene on chromosome 3q27.1 [12]. This gene encodes ClC-2, a voltage-gated chloride channel in zona glomerulosa cells [16]. The mutant gene produces a defective chloride channel with increased permeability, thereby causing depolarization of the cell membrane and influx of calcium intracellularly, resulting in the activation of aldosterone synthesis [18]. Inheritance is thought to be likely autosomal dominant with incomplete penetrance [21]. The gold standard for diagnosis remains genetic analysis, and management of these patients is through the administration of mineralocorticoid receptor (MR) antagonists and unilateral adrenalectomy [16].

- Familial Hyperaldosteronism Type 3 (FH-3)

FH-3 is very rare and occurs secondary to gain-of-function mutations in the KCNJ5 gene located on chromosome 11q24.3 [19, 24]. KCNJ5 encodes for a potassium channel in the zona glomerulosa called GIRK4 which loses its selectivity for potassium with mutations in the gene [22]. This leads to sodium influx into the cells with resultant membrane depolarisation, intracellular calcium entry and aldosterone synthesis [15, 25]. The result is severe hypertension, hypokalemia and bilateral adrenal hyperplasia [16]. Diagnosis is made using genetic testing and adrenal computed tomography [26]. Owing to the variety of phenotypes these patients may present with, bilateral adrenalectomy is recommended in these patients if MR blockers cannot stabilize the blood pressure [25, 27]. Unilateral adrenalectomy has been erroneously trialled in the management of markedly elevated blood pressure and plasma aldosterone in a patient with FH-III [25]. The case highlights the problems faced by managing physicians and the propensity for the development of complications at an early age.

- Familial Hyperaldosteronism Type 4 (FH-4)

This condition results from mutations in CACNA1H, located on chromosome 16p13.3 and encodes the α-subunit of CaV3.2, a T-type calcium channel expressed abundantly in the zona glomerulosa [22, 26]. Wild-type CACNA1H allows the calcium channel to be open transiently [12]. However, the mutant form of the gene impairs the channel's deactivation, resulting in an influx of calcium ions into the zona glomerulosa cells, thus signalling aldosterone synthesis [18].

The disorder is inherited in an autosomal dominant fashion and demonstrates incomplete penetrance with highly variable clinical presentations [19]. FH-4 has no specific treatment, but mineralocorticoid antagonists and adrenalectomy have improved hypertension in these patients [26]. Table 2 below describes the salient characteristics of the familial hyperaldosteronism syndromes.

- Congenital Adrenal Hyperplasia (CAH)

One of the most commonly occurring genetic disorders of the adrenal glands, CAH is a group of autosomal recessive disorders responsible for defects in the pathways of steroid hormone synthesis [23, 28]. The most common of these disorders is 21-hydroxylase deficiency, which accounts for 90-99% of cases [29, 30]. However, these cases do not present with hypertension [23].

11β-hydroxylase deficiency, also known as Type IV CAH, accounts for 5-8% of all CAH cases and is the second most common form of the disorder [12, 31]. It is caused by mutations affecting the CYP11B1 gene on chromosome 8q24.3 [23]. The deficiency prevents the hydroxylation of deoxycorticosterone and deoxycortisol to form corticosterone and cortisol, respectively, thus leading to the accumulation of steroid precursors with a mineralocorticoid effect (especially 11-deoxycorticosterone) [12]. Hypokalemia and low-renin hypertension are secondary to increased sodium reabsorption [17, 31]. Hypertension occurs in at least one-third of cases and is of varying severity [32]. Genetic testing confirms the presence of a mutation in the CYP11B1 gene, but the condition is suspected with elevated basal 11-deoxycortisol [21]. Treatment of hypertension occurs with optimal glucocorticoid replacement; however, MR antagonists such as spironolactone are used alone or with a calcium channel blocker (CCB) when blood pressure control remains inadequate [32].

Type V CAH, caused by 17α-hydroxylase deficiency, is the second form of CAH that can cause low renin hypertension. This rare enzyme deficiency occurs in 1 in 50,000 of the population [31]. Located on chromosome 10q24.32 [12], the defective gene and the resultant loss of enzyme activity cause an increase in the production of deoxycorticosterone and corticosterone at the expense of cortisol and adrenal androgens [31]. The accumulated deoxycorticosterone results in excess mineralocorticoid activity with resultant hypokalemia and hypertension [23]. Molecular testing for the presence of CYP17A1 mutations confirms the diagnosis [32]. MR antagonists help alleviate the hypertension [32].

- Familial Glucocorticoid Resistance (FGR)

Loss-of-function mutations in the NR3C1 gene on chromosome 5q31-q32 [16]. The affected gene encodes the glucocorticoid receptor, rendering it unresponsive to circulating cortisol [17]. The lack of inhibitory feedback on the hypothalamic-pituitary-adrenal axis leads to the overproduction of ACTH, deoxycorticosterone (DOC), corticosterone and

adrenal androgens [33]. This leads to excessive MR activation (as cortisol also has a high affinity for the MR) with subsequent sodium ion overabsorption and hypertension [26].

Patients present with high serum cortisol levels without the peripheral stigmata of Cushing's syndrome, hypokalemia, metabolic alkalosis, and hypertension [34]. Diagnosis is through genetic analysis with background elevated serum cortisol levels [16]. Treatment is through oral dexamethasone, a mineralocorticoid-sparing glucocorticoid [11].

B. Disorders of the Distal Nephron

- Liddle Syndrome

First identified by Liddle et al. in 1963 [16,31], Liddle syndrome is caused by activating (gain-of-function) mutations in the genes (SCNN1A, SCNN1B, SCNN1G) that encode the subunits of the aldosterone-regulated epithelial sodium channels (ENaC) [35,36]. A table collating basic information on the 3 types of Liddle syndrome is attached below (Table 3).

Table 3 Liddle syndrome

TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT
LS-1	16p12.2	SCNN1B	ENaC β-subunit
LS-2	16p12.2	SCNN1G	ENaC γ-subunit
LS-3	12p13.31	SCNN1A	ENaC α-subunit

ENaC – Epithelial sodium channel, LS – Liddle syndrome

Although the worldwide prevalence of the condition is unknown [37], Liddle syndrome is regarded as the most common form of monogenic hypertension [26]. This condition, also known as pseudohyperaldosteronism, is inherited in an autosomal dominant manner with variable penetrance, thus allowing for variability in phenotypes [38–40]. Less than 50 different disease-causing mutations have been identified, with mutations in the SCNN1B gene being the most common [41].

Mutations in the subunits of the ENaCs reduce the rate at which these channels are degraded, leading to increased sodium and water reabsorption and account for hypertension in these patients [42]. Other typical features include hypokalemia, metabolic alkalosis, low serum renin and aldosterone levels [43]. Long-term complications result from hypertension-related organ damage, such as retinopathy, encephalopathy, nephrocalcinosis, cerebrovascular ischemia, left ventricular hypertrophy, and myocardial infarction [42, 44]. Genetic testing allows for early diagnosis of Liddle syndrome and subsequent management [45].

Treatment of hypertension involves dietary sodium limitations and ENaC blockers such as amiloride and triamterene [28, 46].

- Gordon Syndrome

Also known as familial hyperkalemic hypertension or pseudohypoaldosteronism type 2 (PHA2) [45], Gordon syndrome results from mutations identified in 5 different chromosomes [23]. A table detailing these mutations is attached below (Table 4).

PHA2 differs from PHA1, which is associated with hypotension [21]. All five mutations are involved in the regulation of the sodium-chloride cosymporter (NCC) located in the distal nephron [47]. The overall effect of these mutations is the upregulation of the NCC within the distal nephron with increased sodium reabsorption, reduced expression of renal outer medullar K1 channel, and subsequent hyperkalemia and hypertension [31]. Inheritance has been identified to occur in an autosomal dominant or recessive manner, depending on the phenotype [48].

The age of onset of symptoms varies widely [33]. Clinical and laboratory features include hypertension, hypercalcemia, hyperchloremic metabolic acidosis, hypercalciuria and hyperkalemia [49]. A clinical history, laboratory investigations and genetic testing are essential for making a diagnosis [12]. Treatment is achieved by dietary sodium and potassium restriction together with thiazide diuretics as they inhibit the NCC [16].

- Geller Syndrome

Geller syndrome is an autosomal dominant disorder resulting from a gain-of-function mutation in the MR [50]. It is also known as Constitutive Activation of the Mineralocorticoid Receptor or Pregnancy-exacerbated Hypertension which is misleading as the condition also affects non-pregnant females and men [12, 16]. Less than 10 cases have been reported since its initial description in 2000 by Geller et al [50]. The causative mutation affects the hormone-binding domain of the receptor and results from the substitution of leucine for serine at amino acid 810 in chromosome 4q31 [12, 17]. This results in the mutant mineralocorticoid receptor being activated by aldosterone and steroids such as progesterone, a natural antagonist [21]. This receptor is also sensitive to cortisone and 11-dehydrocorticosterone in non-pregnant women and males and spironolactone, which is contraindicated in its management [31, 33].

Patients present with low-renin hypertension at an early age, which worsens with pregnancy, low serum aldosterone and low-to-normal potassium levels [26]. Hypertension and hypokalemia have been noted to peak within the third trimester [17]. Definitive diagnosis, as for a lot of these monogenic disorders, is through genetic testing for the mutations in the MR [50]. Treatment includes limitation of dietary salt, and epithelial sodium channel antagonists such as amiloride and finerenone (a nonsteroidal selective antagonist of the mutant MR) [26, 31, 33]. Close monitoring of fetal and maternal conditions while managing blood pressure and serum potassium levels during pregnancy is the mainstay of treatment [50]. Blood pressure and serum potassium levels return to normal in the postpartum period [17].

- Apparent Mineralocorticoid Excess (AME)

Apparent Mineralocorticoid Excess (AME), more specifically known as Classic AME [51], is an infrequent monogenic hypertensive disorder with about 100 reported

Table 4 Gordon syndrome

TYPE	GENE LOCUS	AFFECTED GENE	GENE PRODUCT	AGE AT DIAGNOSIS	AD/AR	GOF/LOF
PHA2A	1q31-q42	Not known	Not known	Adolescence/Adulthood	AD	-
PHA2B	17q21.2	WNK4	With no lysine kinase 4	Adolescence/Adulthood	AD	LOF
PHA2C	12p13.33	WNK1	With no lysine kinase 1	Adolescence/Adulthood	AD	GOF
PHA2D	5q31.2	KLHL3	Kelch-like 3	Infancy/Childhood	AD, AR	LOF
PHA2E	2q36.2	CUL3	Cullin 3	Infancy/Childhood	AD	LOF

AD – Autosomal dominant, AR – Autosomal recessive, GOF – Gain of function, LOF – Loss of function, PHA – Pesudohypoaldosteronism.

cases worldwide [52]. First reported in the 1970s [53], it was not until 1995 that the first mutation was found [52]. AME is an autosomal recessive disorder caused by a deficiency in the 11β hydroxysteroid dehydrogenase type II enzyme (11βHSD2) secondary to loss-of-function biallelic mutations in the HSD11B2 gene located on the chromosome 16q22.1 [54, 55]. This enzyme is expressed primarily in sodium-transporting epithelia such as the distal nephron [47] and is responsible for the peripheral conversion of cortisol to cortisone [56]. Over 50 pathogenic mutations in the HSD11B2 gene have been reported worldwide [56].

HSD11B2 prevents the activation of the MR by cortisol (which has mineralocorticoid activity) by its conversion to cortisone, which cannot bind to the receptor [12]. With mutations in the gene, cortisol is not metabolized and thus can activate the MR. Affected patients present in infancy with failure to thrive, polyuria, polydipsia, metabolic alkalosis, severe hypertension, hypokalemia, low serum renin, and aldosterone levels [31, 33]. In severe cases, these patients may come down with hypercalciuria, muscle paralysis secondary to severe hypokalemia, renal medullary cysts and nephrocalcinosis [8, 28]. End-organ damage to the heart (LVH), retina (hypertensive retinopathy), central nervous system (stroke) and aortic insufficiency is not uncommon and occurs secondary to hypertension [16, 33].

Diagnosis is ideally through genetic testing, but the 24-hour serum or urinary cortisol to free cortisone ratio is high in these cases [21, 56]. This condition can be mistaken for Bartter syndrome, which can be prevented through blood pressure measurements, serum renin, and aldosterone quantification [36].

Partial deficiency of the 11βHSD2 enzyme (nonclassic AME) presents in adulthood and may be indistinguishable from essential hypertension [31, 36] and is characterized by high serum cortisol to cortisone ratio, normal or slightly elevated blood pressure, normal or low aldosterone and low renin [56]. These patients have elevated microalbuminuria, plasminogen activator inhibitor-1 (PAI-1) and high-sensitivity C-reactive protein (hs-CRP), suggesting that the condition causes a pro-inflammatory state along with vascular and renal problems [51].

Both phenotypes respond to MR antagonists such as spironolactone or eplerenone and a salt-limited diet [56]. Dexamethasone may be used at the lowest effective dose in classic AME to prevent growth retardation [21]. In refractory cases, amiloride and calcium channel blockers may also be prescribed [33]. Renal transplantation has been reported to offer a cure for the condition [12].

Conclusion

Diagnosis of monogenic hypertension syndromes is increasing globally due to the advances in molecular testing techniques. It is plausible that some cases are wrongly diagnosed as primary or essential hypertension when, in fact, they are monogenic in origin. This could lead to a wrongful diagnosis of resistant hypertension, inherently leading to end-organ damage. Physicians catering to adults and children alike should be on the lookout for cases of poorly controlled hypertension associated with biochemical abnormalities, all in the setting of a strong family history. A good history, with specific laboratory investigations and genetic testing (if available), can lead to early diagnosis and reduce morbidity and mortality in these patients. It is also imperative that genetic testing becomes more available and accessible to prevent misdiagnosis.

Author Contributions: Conceptualization, Ug. C. O.; methodology, Ug. C. O.; validation – not applicable; formal analysis, – not applicable; investigation, Ug. C. O. and Uch. C. O; resources research, Ug. C. O., Uch. C. O.; data curation – not applicable; writing – original draft preparation, Ug. C. O.; writing – review and editing, Ug. C. O.; visualization, – not applicable; supervision – not applicable; project administration – not applicable; funding acquisition – not applicable. The authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: None.

References

1. Buffolo F, Monticone S, Pecori A, Pieroni J, Losano I, Cavaglià G, et al. The spectrum of low-renin hypertension. *Best Pract Res Clin Endocrinol Metab*. 2020 May 1; 34(3):101399. https://doi.org/10.1016/j.beem.2020.101399.
2. Zöller B, Manderstedt E, Lind-Halldén C, Halldén C. Rare-variant collapsing analyses of arterial hypertension in the UK biobank. *J Hum Hypertens*. 2023: 1-3. https://doi.org/10.1038/s41371-023-00829-7.
3. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021; 18(11): 785-802. https://doi.org/10.1038/s41569-021-00559-8.
4. Mamdouh H, Alnakhi WK, Hussain HY, Ibrahim GM, Hussein A, Mahmoud I, et al. Prevalence and associated risk factors of hypertension and pre-hypertension among the adult population: findings from the Dubai Household Survey, 2019. *BMC Cardiovasc Disord.* 2022; 22(1): 1-9. https://doi.org/10.1186/s12872-022-02457-4.
5. Lu YT, Fan P, Zhang D, Zhang Y, Meng X, Zhang QY, et al. Overview of Monogenic Forms of Hypertension Combined With Hypokalemia. *Front Pediatr.* 2021; 8: 543309. https://doi.org/10.3389/fped.2020.543309
6. Padmanabhan S, Dominiczak AF. Genomics of hypertension: the road to precision medicine. *Nat Rev Cardiol.* 2021; 18(4): 235-50. https://doi.org/10.1038/s41569-020-00466-4
7. Boder P, Mary S, Mark PB, Leiper J, Dominiczak AF, Padmanabhan S, et al. Mechanistic interactions of uromodulin with the thick ascending limb: perspectives in physiology and hypertension. *J Hypertens*. 2021; 39(8): 1490-504. https://doi.org/10.1097%2FHJH.0000000000002861. PMID: 34187999 PMCID: PMC7611110
8. Yadav M, Sinha A, Hari P, Bagga A. Impaired Distal Tubular Acidification, Renal Cysts and Nephrocalcinosis in Monogenic Hypertension. *Indian J Pediatr.* 2021 Jun 1; 88(6): 579–81. https://doi.org/10.1007/s12098-020-03516-4.
9. Precone V, Krasi G, Guerri G, Stuppia L, Romeo F, Perrone M, et al. Monogenic hypertension. *Acta Bio Medica: Atenei Parmensis.* 2019; 90 (10): 50-52. https://doi.org/10.23750%2Fabm.v90i10-S.8759. PMID: 31577254 PMCID: PMC7233634
10. Lalji R, Tullus K. Causes of Secondary Hypertension in Children and Adolescents. In: Lurbe E, Wühl E, editors. Hypertension in Children and Adolescents. Updates in Hypertension and Cardiovascular Protection. *Springer, Cham.* 2019. p. 111-30 https://doi.org/10.1007/978-3-030-18167-3_8.

11. Lin YF, Peng KY, Chang CH, Hu YH, Wu VC, Chueh JS, et al. Adrenalectomy Completely Cured Hypertension in Patients with Familial Hyperaldosteronism Type i Who Had Somatic KCNJ5 Mutation. *J Clin Endocrinol Metab.* 2019 Nov 1; 104(11): 5462–6. https://doi.org/10.1210/jc.2019-00689.
12. Raina R, Krishnappa V, Das A, Amin H, Radhakrishnan Y, Nair NR, et al. Overview of monogenic or Mendelian forms of hypertension. *Front Pediatr.* 2019 Jul 1; 7: 263. https://doi.org/10.3389/fped.2019.00263.
13. Levanovich PE, Diaczok A, Rossi NF. Clinical and Molecular Perspectives of Monogenic Hypertension. *Curr Hypertens Rev.* 2020; 16(2): 91–107. https://doi.org/10.2174/1573402115666190409115330. PMID: 30963979 PMCID: PMC7499356.
14. Sanga V, Seccia TM, Rossi GP. A systematic review of pathophysiology and management of familial hyperaldosteronism type 1 in pregnancy. *Endocrine*. 2021 Oct; 74(1): 5-10. https://doi.org/10.1007/s12020-021-02763-5.
15. Stowasser M, Wolley M, Wu A, Gordon RD, Schewe J, Stölting G, et al. Pathogenesis of familial hyperaldosteronism type II: new concepts involving anion channels. *Curr Hypertens Rep.* 2019 Apr;21:1-0. https://doi.org/10.1007/s11906-019-0934-y.
16. Park SJ, Shin JI. Diagnosis and Treatment of Monogenic Hypertension in Children. *Yonsei Med J.* 2023 Feb;64(2):77. https://doi.org/10.3349%2Fymj.2022.0316. PMID: 36719014. PMCID: PMC9892546.
17. Garg AK, Parajuli P, Mamillapalli CK. Pregnancy complicated by hypertension and hypokalemia. *American Journal of Kidney Diseases*. 2020 Oct 1; 76(4): A21-2. https://doi.org/10.1053/j.ajkd.2020.04.012.
18. Seidel E, Schewe J, Scholl UI. Genetic causes of primary aldosteronism. *Exp Mol Med*. 2019; 51(11): 1-2. https://doi.org/10.1038/s12276-019-0337-9.
19. Pecori A, Monticone S, Losano I, Cavaglià G, Pieroni J, Veglio F, Mulatero. Familial Hyperaldosteronism. In: Morganti A, Agabiti Rosei E, Mantero F. editors. Secondary Hypertension. Updates in Hypertension and Cardiovascular Protection. *Springer, Cham*. 2020. p. 79-93. https://doi.org/10.1007/978-3-030-45562-0_5.
20. Sanga V, Lenzini L, Seccia TM, Rossi GP. Familial hyperaldosteronism type 1 and pregnancy: successful treatment with low dose dexamethasone. *Blood Press*. 2021; 30(2): 133–7. https://doi.org/10.1080/08037051.2020.1863771.
21. He X, Modi Z, Else T. Hereditary causes of primary aldosteronism and other disorders of apparent excess mineralocorticoid activity. *Gland Surg.* 2020; 9(1):150. https://doi.org/10.21037%2Fgs.2019.11.20. PMID: 32206607 PMCID: PMC7082269.
22. Pons Fernández N, Moreno F, Morata J, Moriano A, León S, De Mingo C, et al. Familial hyperaldosteronism type III a novel case and review of literature. *Rev Endocr Metab Disord.* 2019; 20: 27-36. https://doi.org/10.1007/s11154-018-9481-0.
23. Garofalidou T, Munroe PB. Molecular pathophysiology of systemic hypertension. In: Clinical Molecular Medicine: Principles and Practice. *Elsevier*; 2019. p. 169–87. https://doi.org/10.1016/B978-0-12-809356-6.00011-3.
24. Alam S, Goyal A, Kandasamy D, Bansal VK, Asuri K, Agarwal S, et al. Resistant Hypertension Due to Familial Hyperaldosteronism Type III: First Report From Indian Sub-Continent. *J Endocrine Soc.* 2021; 5 (1): A115-6. https://doi.org/10.1210/jendso/bvab048.314.
25. Takizawa N, Tanaka S, Nishimoto K, Sugiura Y, Suematsu M, Ohe C, et al. Familial Hyperaldosteronism Type 3 with a Rapidly Growing Adrenal Tumor: An In Situ Aldosterone Imaging Study. *Curr Issues Mol Biol*. 2022; 44(1): 128–38. https://doi.org/10.3390/cimb44010010.
26. Mashmoushi A, Wolf MTF. A narrative review of Hyporeninemic hypertension-an indicator for monogenic forms of hypertension. Pediatric Med. 2022; 5: 21. https://doi.org/10.21037%2Fpm-21-48. PMID: 36325202.
27. Mourtzi N, Sertedaki A, Markou A, Piaditis GP, Charmandari E. Unravelling the Genetic Basis of Primary Aldosteronism. *Nutrients*. 2021; 13(3): 875. https://doi.org/10.3390/nu13030875.
28. Raina R, Mahajan Z, Sharma A, Chakraborty R, Mahajan S, Sethi SK, et al. Hypertensive Crisis in Pediatric Patients: An Overview. Front Pediatr. *Frontiers Media S.A.;* 2020; 8: 588911. https://doi.org/10.3389/fped.2020.588911.
29. van der Grinten HLC, Speiser PW, Faisal Ahmed S, Arlt W, Auchus RJ, Falhammar H, et al. Congenital Adrenal Hyperplasia—Current Insights in Pathophysiology, Diagnostics, and Management. Endocr Rev. Endocrine Society; 2022; 43(1): 91–159. https://doi.org/10.1210/endrev/bnab016.
30. Nordenström A, Lajic S, Falhammar H. Long-Term Outcomes of Congenital Adrenal Hyperplasia. Endocrinol Metab (Seoul). *Korean Endocrine Society;* 2022; 37(4): 587-98. https://doi.org/10.3803/EnM.2022.1528.
31. Athimulam S, Lazik N, Bancos I. Low-Renin Hypertension. *Endocrinol Metab Clin North Am.* 2019; 48(4): 701-15. https://doi.org/10.1016/j.ecl.2019.08.003.
32. Tosun BG, Guran T. Congenital adrenal hyperplasia and hypertension. In: Endocrine Hypertension: From Basic Science to Clinical Practice. Elsevier; 2022. p. 113–25. https://doi.org/10.1016/B978-0-323-96120-2.00015-7.
33. Khandelwal P, Deinum J. Monogenic forms of low-renin hypertension: clinical and molecular insights. *Pediatr Nephrol.* 2022; 37(7): 1495–509. https://doi.org/10.1007/s00467-021-05246-x.
34. Martins CS, de Castro M. Generalized and tissue specific glucocorticoid resistance. *Mol Cell Endocrinol.* 2021; 530: 111277. https://doi.org/10.1016/j.mce.2021.111277.
35. Kozina AA, Trofimova TA, Okuneva EG, Baryshnikova N V., Obuhova VA, Krasnenko AY, et al. Liddle syndrome due to a novel mutation in the γsubunit of the epithelial sodium channel (ENaC) in family from Russia: A case report. *BMC Nephrol*. 2019; 20(1): 389. https://doi.org/10.1186/s12882-019-1579-4.
36. Allen GT, Shipman AR, Darragh-Hickey C, Flowers KC, Kaur S, Shipman KE. Investigative algorithms for disorders affecting alkalosis: a narrative review. *J Lab Precis Med*. 2022; 7. https://doi.org/10.21037/jlpm-22-8.
37. Lu YT, Liu XC, Zhou ZM, Zhang D, Sun L, Zhang Y, et al. A Novel Frame-Shift Mutation in SCNN1B Identified in a Chinese Family Characterized by Early-Onset Hypertension. *Front Cardiovasc Med.* 2022; 9: 896564. https://doi.org/10.3389/fcvm.2022.896564.
38. Enslow BT, Stockand JD, Berman JM. Liddle's syndrome mechanisms, diagnosis and management. *Integrated Blood Pressure Control.* 2019: 13-22. https://doi.org/10.2147/IBPC.S188869.
39. Aksoy OY, Bastug F, Celik B, Uytun S. Hypokalemia and hypertensive urgency in a 10-year-old boy: Questions. *Pediatr Nephrol.* 2021; 36(11): 3627–8. https://doi.org/10.1007/s00467-021-05058-z.
40. Mareš Š, Filipovský J, Vlková K, Pešta M, Černá V, Hrabák J, et al. A novel nonsense mutation in the β-subunit of the epithelial sodium channel causing Liddle syndrome. *Blood Press.* 2021; 30(5): 291–9. https://doi.org/10.1080/08037051.2021.1942785.
41. Qu Y, Lu Y, Zhang D, Liu X, Fan P, Chen J, et al. Identification of a novel frameshift mutation in the SCNN1B causing Liddle syndrome. Sci Bull (Beijing). 2023; 68(4): 383–7. https://doi.org/10.1016/j.scib.2023.02.006. PMID: 36774301.
42. Akram S, Rehman A, Khan MA. Liddle Syndrome in a Six-Year-Old Girl: A Case Report. *Journal of Islamabad Medical & Dental College.* 2021; 10(2): 116–9. https://doi.org/10.35787/jimdc.v10i2.642.
43. Steyn N, Chale-Matsau B, Abera AB, Van Biljon G, Pillay TS. Neonatal presentation of a patient with Liddle syndrome, South Africa. *Afr J Lab Med.* 2023; 12(1):1-6. https://dx.doi.org/10.4102/ajlm.v12i1.1998.

44. Brower RK, Ghlichloo IA, Shabgahi V, Elsholz D, Menon RK, Vyas AK. Liddle Syndrome due to a Novel c.1713 Deletion in the Epithelial Sodium Channel β-Subunit in a Normotensive Adolescent. *AACE Clin Case Rep*. 2021; 7(1): 65–8. https://doi.org/10.1016/j.aace.2020.11.017.
45. Yang Y, Wu C, Qu D, Xu X, Chen L, Sun Q, et al. Liddle syndrome misdiagnosed as primary aldosteronism is caused by inaccurate aldosterone-rennin detection while a novel SCNN1G mutation is discovered. *Blood Press.* 2022; 31(1): 139–45. https://doi.org/10.1080/08037051.2022.2088471.
46. Teoh Z, Shah S. A case report of three children with secondary hypertension caused by Liddle syndrome. *Clin Nephrol Case Stud*. 2020; 8(01): 37–40. https://doi.org/10.5414%2FCNCS109972.
47. Pratamawati TM, Alwi I. Summary of Known Genetic and Epigenetic Modification Contributed to Hypertension. *International Journal of Hypertension.* 2023; 2023. https://doi.org/10.1155/2023/5872362.
48. Mabillard H, Sayer JA. The molecular genetics of gordon syndrome. *Genes (Basel)*. 2019; 10(12): 986. https://doi.org/10.3390/genes10120986.
49. Asadi S. The Role Of Genetic Mutations In Genes WNK1,WNK4, CUL3, KLHL3 In Gordon's Syndrome. *Journal of Genetics and Genetic Engineering.* 2019; 3(1): 18–21. https://doi.org/10.3390/genes10120986.
50. Hindosh N, Hindosh R, Dada B, Bal S. Geller Syndrome: A Rare Cause of Persistent Hypokalemia During Pregnancy. *Cureus*. 2022; 14(6). https://doi.org/10.7759/cureus.26272.
51. Carvajal CA, Tapia-Castillo A, Vecchiola A, Baudrand R, Fardella CE. Classic and nonclassic apparent mineralocorticoid excess syndrome. *J Clin Endocrinol Metab.* 2020; 105(4): e924-36. https://doi.org/10.1210/clinem/dgz315.
52. Fan P, Lu YT, Yang KQ, Zhang D, Liu XY, Tian T, et al. Apparent mineralocorticoid excess caused by novel compound heterozygous mutations in HSD11B2 and characterized by early-onset hypertension and hypokalemia. *Endocrine*. 2020; 70(3): 607–15. https://doi.org/10.1007/s12020-020-02460-9.
53. Albalawi AD, Al-Issa SD, AlHissi MA, Aljurayyan AN, Khoder JJ, Al-Jurayyan NA. Hereditary forms of apparent mineralocorticoid excess (AME): Report of a further case and literature review. *World J Biol Pharm Sci.* 2023; 15(1):180–4. https://doi.org/10.30574/wjbphs.2023.15.1.0284.
54. Kucuk N, Yavas Abali Z, Abali S, Canpolat N, Yesil G, Turan S, et al. A rare cause of hypertension in childhood: Questions. *Pediatr Nephrol.* 2020; 35(1): 77–8. https://doi.org/10.1007/s00467-019-04326-3.
55. Verma S, Dabadghao P, Moirangthem A. Apparent mineralocorticoid excess - A rare cause of endocrine hypertension. *Indian Pediatr Case Rep.* 2022; 2(1): 36. https://doi.org/10.4103/ipcares.ipcares_312_21.
56. Lu YT, Zhang D, Zhang QY, Zhou ZM, Yang KQ, Zhou XL, et al. Apparent mineralocorticoid excess: comprehensive overview of molecular genetics. *J Transl Med. BioMed Central Ltd*. 2022; 20(1): 500. https://doi.org/10.1186/s12967-022-03698-9.