Review Article

Mineralocorticoid hypertension

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ABSTRACT

Hypertension affects about 10 – 25% of the population and is an important risk factor for cardiovascular and renal disease. The renin-angiotensin system is frequently implicated in the pathophysiology of hypertension, be it primary or secondary. The prevalence of primary aldosteronism increases with the severity of hypertension, from 2% in patients with grade 1 hypertension to 20% among resistant hypertensives. Mineralcorticoid hypertension includes a spectrum of disorders ranging from renin-producing pathologies (renin-secreting tumors, malignant hypertension, coarctation of aorta), aldosterone-producing pathologies (primary aldosteronism – Conns syndrome, familial hyperaldosteronism 1, 2, and 3), non-aldosterone mineralocorticoid producing pathologies (apparent mineralocorticoid excess syndrome, Liddle syndrome, deoxycorticosterone-secreting tumors, ectopic adrenocorticotropic hormones (ACTH) syndrome, congenitalvadrenal hyperplasia), and drugs with mineraocorticoid activity (locorice, carbenoxole therapy) to glucocorticoid receptor resistance syndromes. Clinical presentation includes hypertension with varying severity, hypokalemia, and alkalosis. Ratio of plasma aldosterone concentraion to plasma renin activity remains the best screening tool. Bilateral adrenal venous sampling is the best diagnostic test coupled with a CT scan. Treatment is either surgical (adrenelectomy) for unilateral adrenal disease versus medical therapy for idiopathic, ambiguous, or bilateral disease. Medical therapy focuses on blood pressure control and correction of hypokalemia using a combination of anti-hypertensives (calcium channel blockers, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers) and potassium-raising therapies (mineralcorticoid receptor antagonist or potassium sparing diuretics). Direct aldosterone synthetase antagonists represent a promising future therapy.

Key words: Aldosterone, aldosteronism, angiotensin, endocrine hypertension, hypertension, inherited hypertension, mineralocorticoid hypertension, renin, secondary hypertension

Introduction

Hypertension affects about 10 – 25% of the population and is an important risk factor for cardiovascular and renal disease.[1] The renin-angiotensin system is frequently incriminated in the etiopathogenesis of hypertension. Hormones that are involved in salt and water retention (mineralocorticoids and glucocorticoids) cause hypertension. Although aldosterone is the main mineralocorticoid incriminated as the causative factor in the genesis of hypertension, a few intermediate products involved in the synthesis of mineralocorticoids can also cause hypertension.

Although mineralocorticoid hypertension remains a useful concept, it is important to realize that the once clear distinction between mineralocorticoid and glucocorticoid steroids no longer exists. The term mineralocorticoid hypertension will be used specifically for causes of hypertension involving an excess production of aldosterone or its intermediate metabolites.

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Historical Review

The adrenal gland was first described by Eustachius in 1563, and its importance was later recognized by the work of Thomas Addison of Guy's Hospital in 1855. He had a particular interest in dermatology and peculiar brown pigmentations of the skin and mucous membranes, which

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he later described as being secondary to adrenal failure, due to tuberculosis. In 1955, Jerome Conn described a disorder constituting high blood pressure, episodes of muscular paralysis associated with very low serum potassium, in which a tumor of the adrenal was detected, which we now commonly refer to as the Conn's syndrome.[2,3]

Anatomy and Physiology of the Adrenal Cortex

The adrenal gland is composed of two embryologically distinct tissues, the cortex and the medulla, arising from the mesoderm and neuroectoderm, respectively. The adrenal cortex is divided into three anatomic zones. The outer zona glomerulosa is the site for mineralocorticoid production. The central zona fasciculate, is responsible mainly for glucocorticoid synthesis and the inner zona reticularis, is the site for adrenal androgen production.[4]

Aldosterone can be considered a final mineralocorticoid product of the renin-angiotensin system (RAS). The cascade begins with the release of renin from the juxtaglomerular (JG) cells of the kidney, in response to decreases in angiotensin II (Ang II) concentrations, distal tubular sodium load (chloride transport across the macula densa), reduced perfusion pressure, or stimulation of $[beta]_1$ receptors. Renin then cleaves angiotensinogen, an [alpha]2-globulin secreted by the liver, to the inactive decapeptide, angiotensin I (Ang 1). This decapeptide can be processed into two different smaller biologically active peptides, Ang II and angiotensin-(1 – 7) {Ang-(1 – 7)}, having opposite actions. Ang-(1 – 7) is formed from Ang I by endopeptidases, including neutral endopeptidase (NEP) and prolylendopeptidas (PEP), while Ang II is generated through an angiotensin-converting enzyme (ACE) Figure 1.

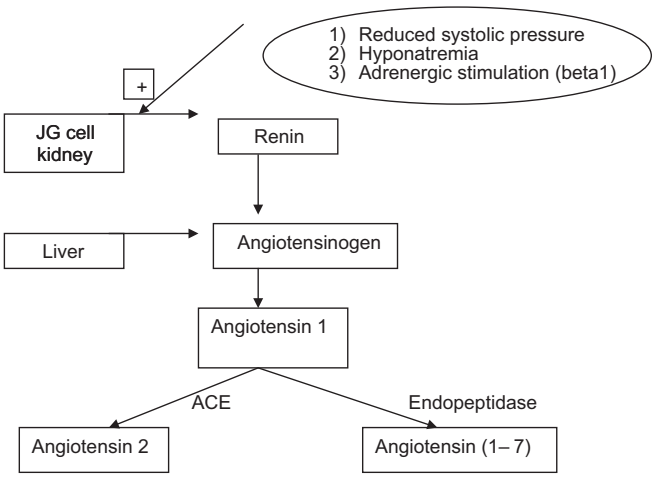


Figure 1: Physiology of RAS

Alternatively, the angiotensin-converting enzyme-2 (ACE2) in the heart, blood, vessels, and renal tissue, can produce Ang-(1 – 7) from Ang I with intermediate formation of Ang-(1 – 9). Therefore, Ang-(1 – 7) can be formed from either Ang I by PEP, prolylcarboxypeptidase (PCP), or ACE2 activity. The *ACE2-Ang-(1 – 7) axis can prevent and even reduce damages observed in cardiovascular disease.*[5-8]

Angiotensin I is then converted to octapeptide angiotensin II by the angiotensin-converting enzyme in the pulmonary vasculature. Angiotensin II (Ang II), the biologically active component of the renin–angiotensin system (RAS), acts through two receptor subtypes, the AT1 and the AT2 receptor. The angiotensin type 1 (AT1) receptor is involved in the classical physiological actions of Ang II; *regulation of blood pressure* (generalized vasoconstriction), *electrolyte and water balance* (modulation of glomerular filtration, facilitation of renal sodium retention at the distal tubular epithelial cells, in exchange for potassium, and hydrogen ion excretion), *thirst* (via AT1 receptors in the hypothalamus and brainstem), and *hormone secretion* (that induces aldosterone and inhibits renin). If aldosterone concentrations are persistently elevated, hypokalaemia, and alkalosis will result in sodium retention (hypertension). The angiotensin type 2 (AT2) receptor is widely expressed in fetal tissues, whereas, its expression is dramatically decreased after birth, being restricted to a few organs such as the brain, adrenals, heart, kidneys, myometrium, and ovaries. It appears to act as a modulator of complex biological processes involved in embryonic development, cell differentiation, tissue repair, and programmed cell death.[9-11]

In addition to the classical pathway leading to Ang II, smaller biologically active angiotensin peptides can be formed from Ang I and II, such as Ang(2 – 8) and Ang(3 – 8) (Ang III and IV) and des[Asp1]-[Ala1]-Ang II (lymphocyte-driven). These peptides are especially formed when the levels of the former are increased during treatment with ACE inhibitors and angiotensin receptor blockers (ARBs). These peptides bind to the AT_1 receptors with a similar affinity as Ang II. Most of these peptides have a greater affinity toward AT2 receptors that stimulate natriuresis and vasodilatation.[12-15]

Renin-Secreting-Tumors

Robertson *et al.* has described the first juxtaglomerular apparatus tumor (renin-secreting). It is associated with severe systolic and diastolic hypertension. Hypertensive retinopathy appears to be common with these tumors. They usually occur in relatively young patients, with a mean age of 24 years (range 7 to 58 years). Renin secretion may also occur as part of the paraneoplastic syndrome (retroperitoneal metastatic leiomyosarcoma, lung carcinoma, acute myeloid leukemia).[16-21]

The metabolic abnormalities appear to be hypokalemia, increased plasma renin activity with or without elevated aldosterone levels, elevated inactive renin (prorenin), and an elevated prorenin-to-renin ratio. Renal venous sampling for a renin assay can be useful (sensitivity approximately (60%). Upright posture and prior frusemide use might improve the sensitivity of renal renin vein sampling.[16-21]

On ultrasound most tumors are hyperechoic, but some are isoechoic or hypoechoic. CT represents the most useful radiological examination to visualize the tumor, with a sensitivity of close to a 100%. A CT scan also permits preoperative diagnosis by direct needle biopsy. Reninomas are either isodense or hypodense, and may become visible only upon enhancement. Tumor size can range from 0.8 to 5 cm. Selective angiography can be associated with high false negative (approximately 40%) and therefore not very helpful.[16-21]

Treatment includes nephrectomy, partial nephrectomy or tumor resection. Perioperative echography is necessary to ensure adequacy of tumor removal as they may have intraparenchymal localization. Conservative surgery is also justified because these tumors are benign, and neither malignant transformation nor local recurrence has been reported.[16-21]

Primary Aldosteronism

Primary aldosteronism (PA) was first described by Jerome Conn[3] in 1955. Primary aldosteronism or Conns syndrome is characterized by hypertension, hypokalemia, and alkalosis. PA is responsible for 10% of all hypertensive cases and it is the most common form of secondary hypertension. The prevalence of primary aldosteronism increases with a severity of hypertension, from 2% in patients with grade 1 hypertension to 20% among resistant hypertensives. Recent studies have, however, reported that only a minority (9 to 37%) are hypokalemic, and thus, the presence of hypokalemia has a low sensitivity and a low-positive predictive value for the diagnosis of primary aldosteronism[3,22-30]

The most common types of PA are:

1. Idiopathic hyperaldosteronism (IHA)
2. Aldosterone-producing adenoma (APA)
3. Bilateral and Unilateral adrenal hyperplasia (UAH)
4. Ectopic aldosterone secreting tumors (ovarian, renal cancer)[31,32]
5. Familial hyperaldosteronism (FH) - Three types
   a. FH 1 (Glucocorticoid remedial hypertension)
   b FH 2 (includes IHA and APA, which is indistinguishable from the sporadic forms of PAL, except that at least two family members are affected by this autosomal dominant inheritance).
   c. FH 3

Idiopathic hyperaldosteronism is generally associated with mild-to-moderate hypertension, hypokalemia (more often normokalemia), and alkalosis. Most hyperaldosteronism in newly diagnosed hypertensive patients is associated with IHA (57%). Bilateral adrenal hyperplasia (smooth, micronodular, or macronodular) occurs generally in older (over 40 years) people. It does not respond to surgical correction and requires long-term medical treatment. Patients with IHA frequently respond to monotherapy with a mineralocorticoid receptor antagonist, but some may require amiloride or other additional antihypertensive medications (angiotensin-converting enzyme inhibitors) for optimal BP control.[22-30]

Aldosterone-producing adenoma is generally associated with moderate-to-severe hypertension, hypokalemia (more severe than IHA), and alkalosis. It accounts for 66% of PA with severe hypertension. Most APAs are benign adenomas. Adrenocortical cancer is very rare. A large tumor size of > 2.5 cm has a higher potential risk for malignancy. Patients with APA are usually younger (less than 40 years). An effective treatment of APAs is adrenalectomy, with the goal of decreasing or eliminating potassium supplementation and antihypertensive medications. Some adenomas may be detected during imaging of nonadrenal-related causes and they are referred to as incidentalomas. Less than 2% of these adenomas are secreting tumors.[22-30]

Unilateral adrenal hyperplasia (UAH), shares many biochemical features with APA. This diagnosis is often made, based on the evidence of the unilateral production of aldosterone (adrenal vein sampling) in the absence of a discrete radiographic mass. In UAH the hypertension and biochemical abnormalities may be cured or ameliorated by unilateral adrenalectomy.[33]

FH 1 (Glucocorticoid remedial aldosteronism (GRA)) — refer to section on GRA

FH 2 includes IHA and APA, which is indistinguishable from the sporadic forms of PA except that at least two family members are affected by this autosomal dominant inheritance.

FH 3 — this represents a new type, characterized by severe hypertension in early childhood. The genetic basis of this disorder is unclear with no abnormality in the aldosterone synthase or 11-[beta] hydroxylase genes identified in the affected subjects.[30] It is associated with

marked hyperaldosteronism, hypokalemia, and significant end-organ damage with a markedly increased production of several adrenal corticosteroids (greater than or equal to 1,000 times the normal), three to four times more than sporadic PA or FH II and 10 times more than FH I. The adrenal gland is strikingly enlarged (three to six times the normal weight) and demonstrates a diffuse hyperplasia of the zona fasciculata and atrophy of the zona glomerulosa. FH 3 responds differently to the dexamethasone suppression test with a paradoxical increase in aldosterone and a lack of suppression of cortisol. They are resistant to aggressive antihypertensive therapy including spironolactone and amiloride, and frequently require bilateral adrenalectomy.[28]

Ectopic Cushing's

In patients with ectopic ACTH secretion (bronchial carcinoid (40%), thymic carcinoid (10%), lung cancer, pancreatic cancer, medullary cancer of the thyroid), hypertension (systolic blood pressure > 140 mmHg and / or diastolic blood pressure > 90 mmHg in adults) is seen in up to 78%. The degree of cortisol secretion is directly related to the severity of hypertension (requiring > 3 anti-hypertrensives) and hypokalemia. The plasma ACTH can vary from 17 – 1557 pg/mL (normal < 60) and 24-hour urine cortisol (UC) excretion from 192 – 1600 mcg / 24 hour (normal < 90). There is no relation between ACTH level and hypokalemia. The current data suggest that high cortisol levels may be the principal cause of hypokalemic alkalosis in Cushing's syndrome, rather than the inhibition of the 11[beta]HSD2 enzyme by ACTH or the effects of adrenal steroid biosynthetic intermediaries with mineralococorticoid activity.[34]

Biochemical Pathways in Production of Mineralocorticoids

Understanding steroidogenesis (production of mineralocorticoid, glucocorticoid, androgens, and estrogens) is of fundamental importance to understanding the disorders of sexual differentiation, reproduction, fertility, hypertension, obesity, and physiological homeostasis.

Steroidogenesis entails processes by which cholesterol is converted to biologically active steroid hormones. The crucial steps are depicted in a comprehensive manner in Figure 2.

The steps involved in the production of mineralocorticoids are:

Cholesterol uptake, storage, and intracellular transport

The human adrenal can synthesize cholesterol *de novo* from acetate, but most of its supply of cholesterol comes from plasma low-density lipoproteins (LDLs) derived from dietary cholesterol. The intracellular cholesterol economy is largely regulated by the sterol response element binding protein (SREBPs). These are a group of transcription factors that regulate genes involved in the biosynthesis of cholesterol and fatty acids. When adequate intracellular quantities of cholesterol are achieved, they help suppress the 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in the synthesis of cholesterol. ACTH increases the availability of free cholesterol for steroid hormone synthesis. Steroidogenesis takes place within the mitochondria. Cholesterol transported to the mitochondia via the steroidogenic acute regulatory protein (StAR), facilitates the movement of cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane, to achieve steroid synthesis.

Most enzymes involved in steroid biosynthesis are either cytochrome P450s (CYPs) or hydroxy-steroid-dehydrogenase's (HSDs). All P450-mediated hydroxylations are mechanistically and physiologically irreversible, whereas, HSD reactions are mechanistically reversible and can run in either direction under certain conditions.[35-39]

Conversion of cholesterol to pregnenolone [Figure 2a]

Conversion of cholesterol to pregnenolone in mitochondria is the first, rate-limiting and hormonally regulated step in the synthesis of all steroid hormones. This process involves three distinct chemical reactions, the 22-hydroxylation of cholesterol, 20-hydroxylation of 22(R)-hydroxycholesterol, and oxidative scission of the C20 – 22 bond of the 20(R), 22(R)-dihydroxycholesterol (the side-chain cleavage (SCC) event) yielding pregnenolone,[40] of which, P450scc (where scc refers to the side chain cleavage of cholesterol) is the most important.[41] Expression of P450scc is induced by cAMP in the adrenal zona fasciculata / reticularis and by the calcium / protein kinase C system in the zona glomerulosa.[42,43]

Conversion of pregnenolone to 17[alpha]-hydroxypregnenolone or progesterone [Figure 2b]

Once pregnenolone is produced from cholesterol, it may undergo 17[alpha]-hydroxylation by P450c17 to yield 17[alpha]-hydroxypregnenolone, or it may be converted to progesterone, the first biologically important steroid in the pathway, via 3[beta]-Hydroxysteroid Dehydrogenase (3[beta]HSD). This 3[beta]HSD converts pregnenolone to progesterone, 17[alpha]-hydroxypregnenolone to 17[alpha]-hydroxyprogesterone (17OHP), Dehydroepiandrosterone (DHEA) to androstenedione, and androstenediol to testosterone. There are two iso-enzymes of 3[beta]-hydroxysteroid dehydrogenase encoded by closely linked

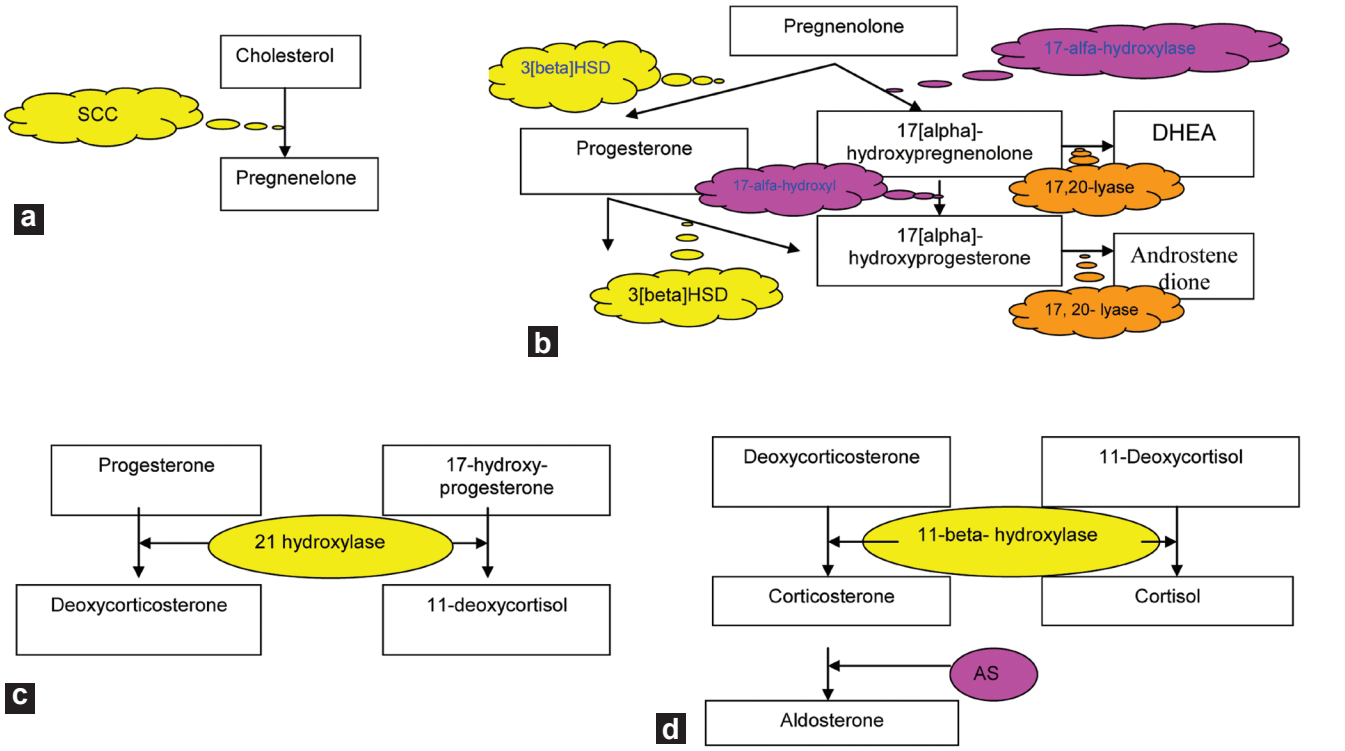


Figure 2: (a-d) Steroid Synthesis (Conversion of Cholesterol to Pregnenolone) in the adrenal cortex. Crucial enzymes are highlighted. Please refer to the text for clinical significance of each step

genes on chromosome 1p13.1. The type 1 enzyme catalyzes 3[beta]HSD activity in the placenta, breast, liver, brain, and some other tissues. The type 2 enzyme (3[beta]HSD2) is the principal isoform in the adrenals and gonads.[44,45]

P450c17 is the microsomal P450 enzyme that catalyzes both 17[alpha]-hydroxylase and 17,20-lyase activities, principally in the adrenal and gonads.

Conversion of Progesterone to 17-Alfa-Hydroxy Progesterone and Pregnenolone to 17-Alfa-Hydroxy Pregnenolone, by 17-Alfa-hydroxylase and 17[Alpha]-Hydroxypregnenolone to Dehydroepiandrostenedione, and 17-Hydroxy Progesterone to Androstenedione, by 17,20lyase [Figure 2b]

P450c17 is the microsomal P450 enzyme that catalyzes both 17[alpha]-hydroxylase and 17,20-lyase activities, principally in the adrenal and gonads. These are two separate individual enzymes catalized at the same site. Their individuality was reinforced with the description of a few patients lacking 17,20-lyase activity, but retaining 17[alpha]-hydroxylase activity.[46-48] Human P450c17 17[alpha]-hydroxylates both pregnenolone and progesterone with approximately equal efficiency to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively. *17,20-lyase* catalyzes the conversion of 17[alpha]-hydroxypregnenolone to DHEA and 17OHP to androstenedione. The 17,20-lyase activity is about 50 times more efficient for the conversion of 17[alpha]-hydroxypregnenolone to DHEA than for the conversion of 17OHP to androstenedione, consistent with large amounts of DHEA secreted by the adult and fetal human adrenal. Because P450c17 has both 17[alpha]-hydroxylase and 17,20-lyase activities, it is the key branch point in the steroid hormone synthesis. Neither activity of P450c17 is present in the adrenal zona glomerulosa; hence, pregnenolone is converted to mineralocorticoids. In the zona fasciculata, the 17[alpha]-hydroxylase activity is present, but 17,20-lyase activity is not; hence, pregnenolone is converted to glucocorticoid cortisol. In the zona reticularis, both activities are present, therefore, pregnenolone is converted to sex steroids.[49,50]

17-Hydroxylase Deficiency

The human gene for 17-alfa hydroxylase has been mapped to chromosome 10(10q24-q25) and consists of eight exons and seven introns. More than 50 distinct mutations causing 17[alpha]-hydroxylase deficiency have been identified. Four mutations appear recurrently: (1) a duplication of four nucleotides causing a frameshift is found among descendents of Dutch Frieslanders; (2) in-frame deletion of residues 487 – 489 is found throughout Southeast Asia; (3) a deletion of phenylalanine at position 53 or 54; and (4) the common W406R and R362C mutations are found

among Brazilians of Spanish and Portuguese ancestry, respectively.[22-25,35,51-57]

Deficient 17[alpha]-hydroxylase activity results in decreased cortisol synthesis, decreased DHEA, androstenedione, and its downstream products (androgens and estrogens), as also an overproduction of metabolites proximal to P450c17 (excess pregnelone, progesterone, and metabolites of mineraloctcicoid axis — deoxycorticosterone, corticosterone, 18-hydroxylated metabolites, and aldosterone). Reduced cortisol causes elevated ACTH and overproduction of aldosterone causes suppression of renin.

Clincial manifestations are secondary to the overproduction or deficiency of metabolites. Mineralcorticoid overactivity causes hypertension, salt retention, and hypokalemia with suppression of plasma renin. Glucocorticoid deficiency is, however, masked by the overproduction of corticosterone, which has glucocorticoid activity. The elevated ACTH that results from the glucocorticoid deficiency, however, results in bilateral adrenal hyperplasia from chronic stimulation. Adrenal sex steroid deficiency can lead to tallness, delayed skeletal maturation, and osteoporosis, during adulthood.

In males: Under-androgenization and absent or reduced masculinization is common. The external genitalia can range phenotypically from normal to infantile to ambiguous.

In females: Milder forms can be associated with normal or irregular menstruation. More severe forms are associated with primary amenorrhea and no pubertal development.

There seems to be no constant correlation between the severity of hypertension and the degree of gonadal insufficiency.[22-25,35,51-57]

Conversion of progesterone to deoxycorticosterone and 17-hydroxy-progesterone to 11-deoxycortisol, by microsomal P450c21 hydroxylase [Figure 2c]

Microsomal P450c21 catalyzes the 21-hydroxylation of the steroid progesterone to DOC and 17OHP to 11-deoxycortisol in the biosynthesis of mineralocorticoids and glucocorticoids, respectively. The nature of this reaction has been of great clinical interest, because 21-hydroxylase deficiency has an incidence of 1 in 15,000 to 1 in 20,000 births, causing more than 90% of all cases of congenital adrenal hyperplasia.[58]

Conversion of deoxycorticosterone to aldosterone and deoxycortisol to cortisol, by P450c11: P450c11[beta] (11-beta-hydroxylase) and P450c11AS (aldosterone synthetase) [Figure 2d]

The final steps in the synthesis of glucocorticoids and mineralocorticoids are catalyzed by two closely related mitochondrial enzymes, P450c11[beta] (11-beta hydroxylase) and P450c11AS (aldosterone synthetase {AS}). The conversion of deoxycorticosterone to aldosterone requires three metabolic steps, 11[beta]-hydroxylase, 18-hydroxylase, and 18 methyl oxidase activities. P450c11[beta] and P450c11AS isozymes are encoded by tandemly duplicated genes on chromosomes 8q21–22 that have 93% amino acid sequence identity.[59]

Of the two isoenzymes P450c11[beta] is more abundant, which converts 11-deoxycortisol to cortisol and deoxycorticosterone to corticosterone, and is expressed predominantly in the zona fasciculata, and to a lesser extent in the zona reticularis, but not in the zona glomerulosa. P450c11[beta] expression is induced by ACTH and is suppressed by glucocorticoids.[35]

The less abundant isozyme, P450c11AS, is found only in the zona glomerulosa, where it has 11[beta]-hydroxylase, 18-hydroxylase, and 18-methyl oxidase (aldosterone synthase) activities. P450c11AS is able to catalyze all the reactions needed to convert deoxycoticosterone to aldosterone. Both enzymes can convert deoxycoticosterone to corticosterone and corticosterone to 18OH-corticosterone, but only P450c11AS can synthesize the aldosterone from 18OH-corticosterone in the zona glomerulosa. The weak 18-hydroxylase activity of P450c11[beta] explains why an adrenal with suppressed P450c11AS expression continues to synthesize 18OH-corticosterone.[35,60,61]

11(beta)-Hydroxylase Deficiency

P450c11[beta] catalyzes the conversion of 11- deoxycortisol to cortisol (zona fasciculata), DOC to corticosterone (fasciculate > glomerulosa), corticosterone to 18-hydroxy-corticosterone (fasciculata > glomerulosa), but has no aldosterone synthetase activity. Deficient 11-hydroxylase activity accounts for about 5 – 8% of congenital adrenal hyperplasia (CAH) in persons of European ancestry and about 15% of cases in both Muslim and Jewish Middle Eastern populations. It has an autosomal recessive mode of inheritance.[22,24,25,62-68]

Deficiency of 11-beta-hydroylase results in the impaired production of glucocorticoids and overproduction of metabolites proximal to the block (deoxycorticosterone, deoxy-cortisol, 17-hydroxy-progesterone, progesterone, pregnelone, and sex steroids). Plasma renin is suppressed and ACTH is elevated causing bilateral adrenal hyperplasia. Overproduction of DOC leads to mineralocorticoid-based hypertension. Although DOC is less potent than aldosterone, patients with 11[beta]-hydroxylase deficiency

may secrete it at high levels, so that salt is retained and the serum sodium remains normal.

The *clinical features* include hypertension, hypokalemia, alkalosis, and salt retention (rarely hypernatremia). Elevated blood pressure is usually not identified until later in childhood or in adolescence, probably due to mineralocorticoid resistance in childhood. Neonatal salt-wasting can be seen with this mutation.[66] Complications of longstanding, uncontrolled hypertension, including cardiomyopathy, retinal vein occlusion, and blindness have been reported in 11β-OHD patients. Malignant hypertension with cerbrovascular accidents have also been reported.[64]
In males: precocious puberty
In females: masculinization, occurs

In contrast to the external genitalia, the gonads and the internal genital structures are normal. Rapid somatic growth in childhood, accelerated skeletal maturation leading to premature closure of the epiphyses, and short adult stature are signs of postnatal androgen excess in both sexes. Affected children may have premature development of sexual and body hair and acne.[67,68]

Non-classical 11β-OHD has been diagnosed in normotensive children with mild virilization or precocious pubarche and in adults with signs of hyperandrogenemia[65]

Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA) represents a rare, heriditary form of primary aldosteronism, which is inherited in an autosomal dominant fashion. In 1966, Sutherland and Laidlaw described a syndrome of hypertension, hyperaldosteronism, and hypokalemia that was found in a family and was reversed by exogenous glucocorticoid therapy. GRA is considered a rare cause of primary aldosteronism, with an estimated incidence of 1 to 3% of the cases.[22-25,69-73]

Glucocorticoid-remediable aldosteronism is caused by a chimeric gene duplication that results from an unequal crossing over between the highly homologous 11[beta]-hydroxylase and aldosterone synthase genes, such that, the chimeric gene represents a fusion of the 11[beta]-hydroxylase gene (expressed normally in the cortisol-producing zona fasciculata) and the 3´ coding sequences of the aldosterone synthase gene (expressed normally in the aldosterone-producing zona glommerulosa). This fusion results in the ectopic overexpression of the chimeric gene in the zona fasciculate, which is under ACTH control.

Although GRA is a mineralocorticoid excess state, normokalemia is the rule in affected individuals, unless provoked by potassium-wasting diuretics. The mechanism for the absence of hypokalemia in GRA is unknown, but there does not appear to be impairment in the renal responsiveness to potassium loading or mineralocorticoid treatment. The hyperaldosteronism in GRA is mild, with distinct diurnal variations under ACTH control probably accounting for the absence of hypokalemia.[71]

Family history is often positive for a history of early hemorrhagic stroke associated with high mortality (61%). The mean age for presentation of stroke is approximately 32 years. The underlying mechanism of the cerebral hemorrhages was thought to be secondary to the intracranial aneurysm. Therefore, screening of asymptomatic GRA patients with magnetic resonance angiography, beginning at puberty and every five years thereafter, is recommended.[72] Hypertension is usually both systolic and diastolic and severe in up to 50% of the children and young adults.

Biochemically, GRA is characterized by detectable normal or high aldosterone, suppressed plasma renin, normoklemia (unless provoked by potassium losing diuretics), elevated aldoerone / renin ratio, up to 30 times elevated 18-oxygenated cortisol compounds (specific for GRA), and easily suppressable aldosterone, to less than 4 ng/dL,[73] post the dexamethasone suppression test.

Metabolism of Cortisol and Corticosterone via Isozymes of 11[beta]-Hydroxysteroid Dehydrogenase (11[beta]HSD)

The interconversion of cortisol to cortisone and corticosterone to 11-deoxycorticosterone is mediated by the two isozymes of 11[beta]HSD, both of which have oxidase and reductase activity, depending on whether $NADP^+$ or NADPH is available as the cofactor. Both enzymes are hydrophobic, membrane-bound proteins that bind cortisol / cortisone and corticosterone / 11-dehydrocorticosterone.[74]

The type 1 enzyme (11[beta]HSD1) is a dimer of 34-kDa subunits expressed mainly in glucocorticoid-responsive tissues, such as, the liver, testis, lung, fat, and proximal convoluted tubule. The type 1 enzyme catalyzes both the oxidation of cortisol to cortisone using $NADP^+$ as the cofactor and the reduction of cortisone to cortisol using NADPH as the cofactor. It seems that this enzyme functions primarily as a reductase resulting in the inactivation of cortisol to cortisone *in vivo*. The corresponding human

gene for this isozyme, *HSD11B1* (*HSD11L*) is located on chromosome 1. Many synthetic glucocorticoids (e.g., prednisone and cortisone) are 11-ketosteroids that must be reduced to their 11[beta]-hydroxy derivatives to attain biological activity, which is performed mainly in the liver by 11[beta]HSD1.[75-77]

Type 2 enzyme[78] (11[beta]HSD2) is a 41-kDa protein that has only 21% sequence identity with 11[beta]HSD1. 1[beta] HSD2 catalyzes only the oxidation of cortisol to cortisone and corticosterone to 11-dehrdocortixosterone using NAD^+ 11[beta]HSD2, which is expressed in mineralocorticoid-responsive tissues (kidneys, placenta, salivary gland, colon). Corticosterone is the preferred substrate. It has a 10 times higher affinity for corticosterone than for cortisol. It thus serves to 'defend' the mineralocorticoid receptor by inactivating cortisol to cortisone, so that only 'true' mineralocorticoids such as DOC can exert a mineralocorticoid effect. It preferentially favors the dehydrogenase reaction (cortisol to cortisone). Inactivating mutations in the type 2 enzyme therefore result in increased cortisol, relative to cortisone. Cortisol half-life in the plasma is prolonged from approximately 80 minutes to 120 to 190 minutes. The resultant activation of the mineralocorticoid receptor causes hypertension (hypokalemia and alkalosis), resulting in a syndrome of apparent mineralocorticoid excess (AME).

The placenta also has abundant $NADP^+$ favoring the oxidative action of 11[beta]HSD1. Hence, in the placenta, both enzymes protect the fetus from high maternal concentrations of cortisol.[79] Cortisol is a potent agonist at the mineralocorticoid receptor in the distal nephron, but its oxidized 11-keto derivative, cortisone, is not a mineralocorticoid.[80]

The Syndrome of Apparent Mineralocorticoid Excess

Apparent mineralocorticoid excess was first described in detail by Ulick and colleagues.[81] It has an autosomal recessive mode of inheritance. In AME or licorice intoxication, 11-HSD deficiency allows the cortisol to occupy the mineralocorticoid receptor. As the cortisol normally circulates at levels 100 to 1000 times those of aldosterone, it leads to signs of mineralocorticoid excess, even though aldosterone secretion is suppressed.[35,22-25,80,81]

Children present with hypertension, hypokalemia, and low plasma renin activity. Often severe hypokalemia can cause nephrocalcinosis, nephrogenic diabetes insipidus, and rhabdomyolysis. Complications of hypertension have included cerebrovascular accidents (10%), and several patients have died during infancy or adolescence. Intrauterine growth retardation and postnatal failure to thrive can complicate AME.[35,22-25,80,81]

Liddle Syndrome

Liddle syndrome is a rare form of autosomal dominant hypertension with early penetrance and impressive cardiovascular sequelae. The basic features of this syndrome were described in a large kindred from Alabama by Grant Liddle and co-workers, in 1963.[22-24,82-85]

The subunits of the epithelial sodium channel (ENaC) complex on the collecting tubule of a nephron, have been recognized as important candidates for the cause of the Liddle syndrome. The ENaC complex is composed of three homologous subunits (alfa, beta, gamma). The genetic linkage analysis has identified a causal mutation in the [beta] subunit of the amiloride-sensitive Na^+ channel as the causative factor. Defined mutations in pedigrees with Liddle syndrome, fall within a very narrow range of 30 amino acids of the cytosolic tail of the [beta] subunit. An analogous mutation to that in the original pedigree ([beta] R564X) has been described in the [gamma], but not in the [alpha] subunit in any human.[83,84]

Liddle syndrome is an extreme example of low-renin, volume-expanded hypertension. The original index case described by Liddle developed renal failure, in 1989, and underwent successful renal transplation.

Despite a clinical presentation, typical of primary aldosteronism, the actual rates of aldosterone excretion were markedly suppressed, accounting for the descriptive term 'pseudoaldosteronism'. Hypertension can be severe when associated with low renin and low aldosterone concentrations. Renal failure, cerebrovascular complications, and chronic complications of hypokalemia can occur.

Typically patients do not respond to steroid therapy or spironolactine. Instead they respond well to inhibitors of epithelial sodium transport such as triamterene.

Familial Glucocorticoid Resistance Syndrome

Familial glucocorticoid resistance (FGR) is caused by mutations in the [alpha]-isoform of the glucorticoid receptor. Patients may be homozygous for missense mutations or heterozygous for a gene deletion. Homozygous frameshift mutations and heterozygous point mutations interfere with the GR[alpha]-dependent transcriptional regulation through altered DNA binding, impaired ligand binding,

delayed nuclear localization, abnormal nuclear aggregation, and disrupted interaction with co-activators, depending on the position of the mutation. Peripheral glucocorticoid resistance, results in grossly increased ACTH secretion. This in turn leads to excess production of cortisol, mineralcocorticoids, and sex steroids. Clinical presentation includes fatigue, hypertension, and hypokalemic alkalosis, suggesting a mineralocorticoid excess syndrome. Excess sex steroids can lead to varying degrees of hyperandrogenism. Familial glucocorticoid resistance is typically a syndrome of only partial resistance to the action of glucocorticoids.[86-88]

Who Should be Screened for Mineralocorticoid Hypertension?

Patients with:

1. Blood pressure > 160 / 100 particularly (< 50 years)
2. Resistant hypertension or refractory hypertension (use of > 3 anti-hypertensives and poor control of blood pressure)
3. Hypokalemia (provoked by diuretic therapy or unprovoked)
4. Hypertension and incidentally discovered adrenal adenoma
5. Hypertension with a family history of early-onset hypertension (< 20 years) or cerebrovascular accident at age less than 40 years
6. Hypertensive first-degree relatives of patients with PA [26]

Approach

1. Case detection (screening)
2. Case confirmation
3. Subtype classification

Case detection (screening): Aldosteronism is initially screened by measuring plasma aldosterone (PA), plasma renin activity (PRA) or direct renin concentration and plasma aldosterone concentration / plasma renin activity (PAC / PRA). The tests should be performed between 8 a.m. and 10 a. m., with two to four hours of ambulation or being upright, and then sitting for approximately 10 minutes before testing.[89] A PAC / PRA ratio of > 30 is strongly suggestive of PA and a ratio of > 50 is virtually diagnostic of PA.[90] Compared to PAC / PRA, the use of PAC / plasma renin concentration (direct) is equally effective in the diagnosis of primary aldosteronism, with an optimal cut-off value of 27.3 ng/mIU, which is remarkably similar to that previously determined for the aldosterone–renin ratio based on PRA.[91]

As hypokalemia can impair aldosterone secretion it is prudent to adequately replace potassium before testing. Ideally drugs that affect the renin–angiotensin axis should be withdrawn prior to testing, such as: beta-blockers, ACE inhibitors, ARBs (angiotensin receptor blockers), renin inhibitors, dihydropyridine calcium channel blockers, and central alpha2-agonists, for approximately two weeks, and spironolactone, eplerenone, amiloride, and triamterene, and loop diuretics for approximately four weeks. Often this is not practically possible and drugs other than spironolactone and eplerenone, and direct renin inhibitors and amiloride (> 5 mg) can be continued. When on ACE inhibitor, ARB or diuretic if the PRA is suppressed < 1 ng / ml, primary aldosteronism should be highly suspected. Significant false-negative results have, however, been reported in patients taking amlodipine (1.8%) and irbesartan (23.5%).[92] Although adrenergic inhibitors (beta-blockers and central alfa2 agonists) suppress renin secretion, they also reduce aldosterone secretion leaving the PAC / PRA relatively unaffected.

Conditions associated with suppressed plasma renin and suppressed plasma aldosterone concentration (suggesting alternate source of mineralocorticoid agonism):

1. Exogenous mineralocorticoid (licorice, carbenoxolone)
2. Ectopic ACTH producing tumor (Cushing's syndrome)
3. Liddle syndrome
4. Congenital adrenal hyperplasia (11-beta-hydroxylase deficiency, 17-hydroxylase deficiency)
5. Apparent mineralocorticoid excess syndrome
6. Deoxycorticosterone secreting tumor

Conditions associated with suppressed plasma renin, elevated plasma aldosterone concentration (PAC> 20 ng / dl {> 555 pmol / L in S.I. unit} and PAC / PRA ratio > 30 {> 832 in S.I. units} has a sensitivity of 90% and a specificity of 91% for the diagnosis of primary aldosternoism):

1. Aldosterone secreting adenoma,
2. Bilateral adrenal hyperplasia
3. GRA
4. Aldosterone secreting carcinoma
5. Uunilateral adrenal hyperplasia
6. Familial hyperaldosteronism 2 and 3).[93]

Conditions associated with elevated plasma renin and plasma aldosterone concentration (with PAC / PRA < 10 {277 in S.I. units}):

1. Renin-secreting tumors
2. Diuretic use
3. Renovascular hypertension
4. Coarctation of aorta
5. Malignant phase hypertension

Aldosterone, 1 ng / dl converts to 27.7 pmol / liter in Systèm International (SI) units. For immunometric methods of directly measuring renin concentration, a

PRA level of 1 ng / ml· / hour (12.8 pmol / liter· / minute in SI units) converts to a direct renin concentration of approximately 8.2 mU / liter (5.2 ng / liter in traditional units) when measured either by the Nichols Institute Diagnostics automated chemiluminescence immunoassay (previously widely used, but recently withdrawn) or the Bio-Rad Renin II radioimmunoassay.[26]

Case confirmation: Once primary aldosteronism is suspected, case confirmation is recommended using one of the following well-validated tests (1 – 4):

1. *Fludrocortisone suppression test (FST)* (upright plasma aldosterone levels measured at 10:00 hours after four days administration of the synthetic mineralocorticoid 9-[alpha]-fludrocortisone acetate (0.1 mg every six hours) and sodium chloride [slow-release sodium 30 mmol (1.75 g) thrice daily], with a value of > 6 ng / dl and concomitant PRA levels < than 1.0 ng / ml / hour, confirming primary hyperaldosteronism).[94]
2. *Intravenous saline load test (SLT)* (infusion of two liters of NaCl 0.9% fours hours with PAC more than 10 ng / dl is diagnostic, normally aldosterone suppresses to below 5 ng / dl. It is contraindicated in patients with severe hypertension, chronic kidney failure, heart failure, cardiac dysrhythmias, or severe hypokalemia)[26,95]
3. *Oral sodium loading test* (High sodium diet, of approximately 218 mmol / day, for three days. On the last day of the high-salt diet, patients are required to collect a 24-hour urine sample. Normal suppression is defined as post-test 24-hour urinary aldosterone excretion less than 12 μg / day, with concomitant urinary sodium excretion of more than 200 mmol / day, to document adequate sodium repletion. It has > 90% sensitivity and specificity).[94]
4. *Captopril challenge test* (PAC / PRA > 30, measured two hours after the administration of 25 mg or 50 mg of captopril with patients in the sitting position, has been proposed as a diagnostic cut-off value for primary aldosteronism)[26,94,96]

Other less validated tests

5. Frusemide upright posture test
6. 24-hour urinary aldosterone
7. Losartan test

The fludrocortisone suppression test is regarded as the gold standard test for the confirmation of primary aldosteronism. When SLT was compared with the efficacy of FST, SLT was found to have a high positive predictive value (92%) with high sensitivity and specificity (90 and 84%, respectively) and could be considered an effective option to the FST.[95]

Three hundred and seventeen patients were prospectively studied, to assess the efficacy of the captopril test over SLT, and it was found that the accuracy of the SLT surpassed that of the capropril test in patients with a sodium intake < = 130 mEq per day; both the captopril test and the SLT were equally safe and moderately accurate for excluding primary aldosteronism (APA) in patients with a sodium intake > 7.6 g per day. The optimal aldosterone cutoff value for identifying APA was 13.9 and 6.75 ng/dL for the captopril test and SLT, respectively.[96]

A number of false-positive and false-negative diagnoses have been found with the captopril test, and therefore, they are reserved for patients with reduced cardiac or renal function.[97]

Subtype Classification: Once the diagnosis is confirmed a subtype classification is required as the treatment strategies vary depending on the etiology. Young age (< 50 years old), severe hypokalemia (< 3.0 mmol / L), high plasma aldosterone concentrations (> 25 ng / dl), and high urinary aldosterone excretion (> 30 ug / 24 hours) favor the diagnosis of APA versus bilateral adrenal hyperplasia. Although useful they lack specificity, and therefore, cannot be relied on.[26,33,90]

Tests useful in assessing subtypes are:

1. ***Computed Tomography (CT)*** — A high-resolution CT (HRCT) scan with contrast, with fine cuts (2.5 – 3 mm), is the imaging technique that displays the best sensitivity and specificity in identifying adrenal nodules. CT alone is inadequate for the differential diagnosis between APA and bilateral adrenal hyperplasia. The diagnostic performance of CT (sensitivity 40 to 100%) depends on the size of the APA lesion, being greatest for lesions > 2 cm. The yield for detecting APA less than 1 cm in diameter is lower, and is reported to be around 25%. It cannot distinguish between a functional APA and a non-secreting adrenal adenoma (incidentaloma). A unilateral lesion exceeding 4 cm suggests possible carcinoma.[94,98,99]
2. ***Magnetic Resonance Imaging (MRI)*** — sensitivity of 70 to 100% in detecting APA, depending on the size of the lesion, being greatest for lesions > 2 cm. It shares the same problems as encountered in the CT scan.
3. ***Adrenal venous sampling (AVS)*** — The endocrine society recommends this as the gold standard test. The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess is superior to that of the adrenal CT (78 and 75%, respectively). The procedure although very useful, is expertise-dependant. The right adrenal vein (smaller than the left and usually empties directly into the IVC rather than the renal vein) is more difficult to cannulated, with success rates for cannulating the right adrenal vein

ranging from 74[100] to 90 – 96%,[26] increasing with experience. The risk of adrenal hemorrhage is very rare and the complication rate is 2.5% or lower. AVS can be performed using any of the three protocols, (1) unstimulated sequential or simultaneous bilateral AVS, (2) unstimulated sequential or simultaneous bilateral AVS followed by bolus cosyntropin-stimulated sequential or simultaneous bilateral AVS, and (3) continuous cosyntropin infusion with sequential bilateral AVS. Plasma aldosterone collected from the adrenal veins is corrected to its respective plasma cortisol, measured as a ratio (PAC / cortisol ratio), in order to counter the possible dilutional effect of the samples. A gradient of > 4:1, from the high to the low side suggests unilateral aldosterone secreting pathology and < 3 : 1 suggests bilateral adrenal hyperplasia.[26,95,98,101] Using these criteria, AVS has a sensitivity of 95% and a specificity of 100% to detect unilateral disease. The minimum gradient suggested by one study was 2.75.[102]

4. ***Posture stimulation test*** — can be used when AVS is unrewarding. Developed in the 1970s, it was based on the principal that PAC in patients with APA showed diurnal variation and was relatively unaffected by changes in the angiotensin II levels being under ACTH control, whereas, IHA was characterized by enhanced sensitivity to a small change in the angiotensin II, which occurred with standing. A review of 16 published reports demonstrated an accuracy of 85% for APA.[26,100,103]
5. ***Iodocholesterol scintigraphy*** — [6[beta]-^{131}I] iodomethyl-19-norcholesterol (NP-59), was introduced in 1977 for the diagnosis for primary aldosteronism. The NP-59 scan, performed with dexamethasone suppression, had the putative advantage of correlating function with anatomical abnormalities. However, because the tracer uptake was poor in adenomas smaller than 1.5 cm in diameter, this method was often not helpful in interpreting micronodular findings and is currently no longer used in most centers.[104]
6. ***18-Hydroxycorticosterone levels*** — Formed from 18-hydroxylation of corticosterone it was traditionally used to differentiate APA from bilateral adrenal hyperplasia. Recumbent plasma 18-hydroxycorticosterone levels greater than 100 ng/dl at 8 a.m., suggested APA. However, it lacked accuracy.[105]

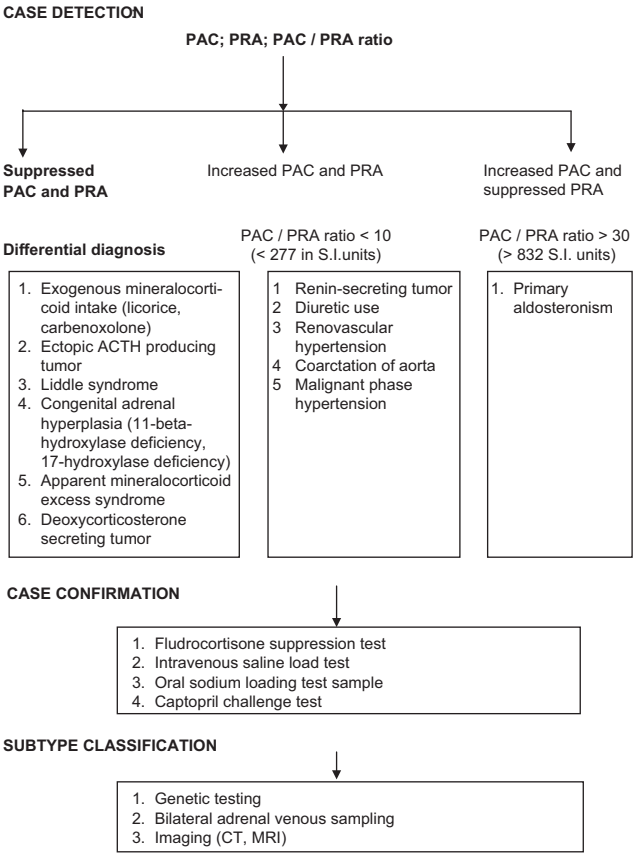
Genetic testing

Genetic testing should be considered for PA patients with a family history of PA, strokes in young (< 40 years),[26,106] or with hypertension, with onset at young age (e.g., < 20 years). Genetic testing for GRA by either Southern blot or long polymerase chain reaction (PCR) techniques is sensitive and specific.

Algorithm for approach to patient with suspected aldosteronism

Appropriate clinical presentation

1. BP > 160 / 100 in patients < 50 years
2. Resistant hypertension or refractory hypertension (use of > 3 anti-hypertensives)
3. Hypokalaemia (provoked by diuretic therapy or unprovoked)
4. Hypertension adrenal incidentaloma
5. Hypertension with a family history of early-onset hypertension (< 20 years) or cerebrovascular accident at age less than 40 years.
6. Hypertensive first-degree relatives of patients with PA



Treatment

Once the diagnosis and subtype of primary aldosteronism is confirmed, the appropriate therapy should be initiated.

1. **Surgical therapy** — indicated for unilateral adrenal hyperplasia, APA, adrenal carcinoma, ectopic ACTH, renin, and deoxycorticosterone secreting tumors. Laproscopic adrenalectomy is the procedure of choice for adrenal lesions. The percentage of cure

in different studies ranges between 30 and 60%, whereas, an improvement is observed in all patients. Blood pressure tends to show maximal improvement one to six months postoperatively. Factors reported to predict cure after adrenalectomy are, response to spironolactone therapy, younger age, shorter duration of hypertension, family history of hypertension in at least one first-degree relative, preoperative use of at least two antihypertensive agents, higher PAC / PRA and 24-h urinary aldosterone levels.[26,107] Preoperatively hypertension and hypokalemia should be controlled adequately. Postoperatively anti-hypertensives and anti-hypokalemics should be withdrawn and only be used on an, 'as and when required' basis. Anti-hypokalemics can be continued if serum potassium is < 3.0 meq / l. PAC / PRA should be measured immediately postoperatively on day one, to ensure adequacy of surgical cure. A dynamic test such as FST or SLT can be conducted three months after surgery.

1. **Medical therapy —** indicated for bilateral adrenal hyperplasia and all equivocal causes of primary aldosteronism
   a. **Mineralocorticoid receptor antagonists —** are spironolactone, potassium canrenoate, and eplerenone. The first two have affinity for androgen and progesterone receptors, causing side effects such as, gynecomastia (6.9% at dose < 50 mg / day and 52% at dose > 150 mg / day),[108] sexual dysfunction, and menstrual irregularities. Spironolacone is used at a starting dose of 12.5 – 25 mg twice daily and increased gradually to a maximum of 400 mg per day. Eplerenone is a selective mineralcorticoid receptor antagonist without antiandrogen and progesterone agonist activity. It is 60% as potent as spironolactone and should be administered twice daily because of its short half life. It has been shown to be as effective as spironolactone.
   b. **Potassium-sparing diuretics —** amiloride, triamterene. Potassium-sparing diuretics, such as triamterene or amiloride, have been used, although they are usually not as effective as spironolactone
   c. **Other anti-hypertensives —** calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and low doses of thiadzides diuretics.

Liddle syndrome is treated using triamterene. FH-I therapy is etiologically based on (0.5 – 0.75 mg / day) dexamethasone therapy. FH-II patients should be managed in the same way as those with sporadic primary aldosteronism, that is, adrenalectomy for APAs and mineralocorticoid treatment for bilateral adrenal hyperplasia. For FH-III the data is limited to a single family. Use of bilateral adrenalectomy results in a reduction of blood-pressure levels.

An orally active aldosterone synthase inhibitor (LCI699) in doses up to 1.0 mg BID, effectively and safely inhibited aldosterone synthase and corrected hypokalemia, causing a mild decrease in blood pressure. It represented a possible future therapeutic strategy for primary aldosteronism.[109]

Conclusion

Although challenging, the diagnosis of primary aldosteronism can be rewarding both to the patient and the treating physician. Chronic hypertension and hypokalemia can be either reversed (surgically) or effectively controlled (medically), thereby preventing long-term complications. Prenatal diagnosis of inheritable monogenic causes of mineralocorticoid hypertension (GRA) is equally important in order to diagnose and prevent future cerebrovascular and cardiovascular complications. The future holds a lot of promise with therapies such as aldosterone synthetase inhibitors on the horizon.

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