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Review Article

Endocrine Hypertension: Diagnosis and Approach

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Abstract

Hypertension is a major public health problem affecting more than one-third of adults above the age of 18 years.[1] Hypertension is one of biggest contributors to the global burden of disease and mortality.

Key words: Aldosterone-producing adenoma , hypokalemia, adrenal hypoplasia

Introduction

Hypertension is a major public health problem affecting more than one-third of adults above the age of 18 years.[1] Hypertension is one of biggest contributors to the global burden of disease and mortality. In adults, hypertension is primarily idiopathic while secondary hypertension occurs in 10–15% of subjects. 57% of hypertensive children attending tertiary care center have secondary hypertension while 6% have endocrine hypertension.[2] In subjects, 18–40 years attending referral hospitals, secondary hypertension occurs in almost 30% of subjects; primary hyperaldosteronism 7.4%, fibromuscular dysplasia 5.8%, and pheochromocytoma in 3.9% of patients.[3]

At least 15 endocrine conditions can present to clinician as hypertension. Recognition of appropriate protocol based diagnosis is the key to medical or surgical cure of causative endocrine disorder. In this article, we review the clinical presentation, prevalence, the case detection approach, diagnostic protocol, and treatment.

Primary Hyperaldosteronism

Unregulated excessive production of aldosterone from adrenal gland leads to hypertension, hypokalemia, metabolic alkalosis, and suppressed renin-angiotensin axis. Primary aldosteronism (PA) causes significant cardiovascular, cerebrovascular, and renal morbidity, which is disproportionate to the degree of hypertension.[4] Primary hyperaldosteronism accounts for 5–10% of hypertensive subjects while in resistant hypertensive subjects, 20% of subjects. It is now widely acknowledged that majority of subjects with PA are normokalemic.[5] Most patients with PA are diagnosed during their 3–6th decades. Patients with PA also display an increased prevalence of metabolic syndrome and diabetes, osteoporotic fractures, and symptoms of depression with a reduced quality of life. Aldosterone-producing adenoma (APA) and bilateral idiopathic hyperaldosteronism (IHA) are the most frequent causes of PA, accounting for 90% of cases. Primary (unilateral) adrenal hyperplasia constitutes 2% of cases, aldosterone-producing adrenocortical carcinoma constitutes <1% of cases while familial hyperaldosteronism (FH) is constituted by glucocorticoid-remediable aldosteronism (GRA, FH type 1, <1%), FH type 2 (APA or IHA, <6%), and FH type 3 (germline KCNJ5 mutations, <1%). Very rarely, ectopic APA or carcinoma (<0.1%) is found.

Pathophysiology

Aldosterone is synthesized from cholesterol in the zona glomerulosa (ZG) of the adrenal cortex by a series of locus- and orientation-specific enzymatic reaction catalyzed by dehydrogenases and mixed-function oxidases. Many of these enzymes belong to the cytochrome P450 superfamily of heme-containing enzymes.

Aldosterone synthesis and secretion are principally regulated by angiotensin II (Ang II), serum K+ levels, and ACTH hormone. However, other regulators are adrenaline, vasoactive

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intestinal polypeptide, serotonin, ouabain, atrial natriuretic peptide, dopamine, heparin, and adrenomedullin.

In renin-angiotensin system, renin is synthesized and released by the juxtaglomerular cells in the afferent arteriole of the kidney in response to a decrease in intravascular volume detected by baroreceptors (mediated by β-adrenoreceptor activation) and by a reduced sodium concentration at the macula densa. Renin catalyzes the hydrolysis of angiotensinogen to angiotensin I (Ang I) which is then converted to Ang II by angiotensin-converting enzyme, presents in the lungs and vascular tissue. Ang II acts on vascular smooth muscle to cause vasoconstriction and on the adrenal ZG to stimulate aldosterone production. The acute adrenal response to Ang II occurs within minutes, implying the release of preformed aldosterone, and possibly rapid synthesis of aldosterone. Chronic stimulation by Ang II results in ZG hypertrophy and hyperplasia increased *CYP11B2* expression and subsequent aldosterone secretion. Ang II stimulates aldosterone production through specific G-protein-coupled receptors (AT1 receptors).

Aldosterone secretion is acutely sensitive to minute changes in extracellular K^+ concentration. Increased $[K^+]$ concentration stimulates aldosterone secretion. The effects of extracellular $[K^+]$ and Ang II are synergistic so that the prevailing $[K^+]$ determines the concentration/effect relationship for Ang II-mediated aldosterone production. Ang II and K^+ regulate *CYP11B2* transcription through common Ca^{2+}-dependent signaling pathways and also through many common transcription factors.

Acutely, ACTH stimulates aldosterone production through cAMP-mediated pathways and multiple protein synthesis-independent mechanisms. In contrast, chronic ACTH stimulation suppresses plasma aldosterone levels in both humans and animal models. The mechanism of chronic inhibition is unclear; the postulated pathways are downregulation of Ang II receptors in adrenocortical cells by cAMP, transformation of ZG cells into zona fasciculate, or diversion of precursors from the mineralocorticoid to the glucocorticoid pathway.

The effects of aldosterone are mediated by mineralocorticoid receptors (MRs) located in the renal cell cytosol. These belong to the nuclear receptor superfamily and are composed of several functional domains. Hormone-binding results in a conformational change resulting in dissociation of the associated proteins, dimerization and translocation to the cell nucleus, and binding to steroid-responsive elements in the 5'UTR of aldosterone-responsive genes that activate or repress gene transcription. The epithelial action of aldosterone consists of early (1–6 h) and late (>6 h) phases.

MR receptors are present in renal cytosol, salivary glands, and colon. Type 2 glucocorticoid receptors (GRs) are expressed ubiquitously and have higher affinity for glucocorticoids such as cortisol and corticosterone. There is a high degree of homology between MRs and GRs in their DNA-binding domains (94%) and ligand-binding domains (57%), and hence, MRs have high affinity to glucocorticoids. 1β-HSD type 2 (11β-HSD2) enzyme complex colocalizes with MRs in target epithelial tissues. This enzyme catalyzes the conversion of active glucocorticoids, capable of binding with high affinity to MRs, into inactive metabolites (in humans, this is the conversion of cortisol to cortisone). These metabolites have little affinity for the MR and so the action of 11β-HSD2 effectively protects the MR from illicit occupation by glucocorticoids. This protective phenomenon is clinically important in syndrome of apparent mineralocorticoid excess. It is characterized by sodium retention, hypokalemia low renin, and hypertension, in the absence of excessive aldosterone or 11-deoxycorticosterone (DOC), and is due to excessive consumption of liquorice, a component of which - glycyrrhetinic acid - inhibits 11β-HSD2. In mutation of gene for this enzyme, which is inherited as autosomal recessive disorder, results in inactive 11β-HSD2 enzyme and similar picture but is successfully treated with dexamethasone, which suppresses endogenous cortisol and does not bind to MR.

Clinical Picture

There are no specific symptoms or signs of PA; however, there is a need for suspicion of this diagnosis in following situations; hypertension with spontaneous or diuretic-induced hypokalemia, resistant hypertension, hypertension with adrenal incidentaloma, severe hypertension (systolic >160 mmHg or diastolic pressure >100 mmHg), suspicion of secondary hypertension, and onset of hypertension at young age (<20 years).[6] Patients with significant hypokalemia can have muscle weakness, muscular cramps, headache, palpitations, polyuria, polydipsia, or tetany, either in combination or in isolation. Periodic paralysis with hypokalemia is a common presentation in Indian and subjects from Southeast Asians descent but rare in Caucasians.

In general, patients with APAs have more severe hypertension, more frequent hypokalemia, higher levels of plasma aldosterone (>25 ng/dL) and urinary aldosterone (>30 μg/24 h), and are younger (<50 years), compared with those who have IHA.

Diagnosis

The diagnostic approach to PA is generally considered as three-step approaches: Case detection tests, confirmatory tests, and then subtype evaluation tests.[6]

Case Detection

Screening for PA is usually accomplished with the estimation of the ratio of plasma aldosterone concentration (PAC, ng/dL) to plasma renin activity (PRA, ng/mL/h) by obtaining paired random ambulatory morning (preferably at 8–10 am) blood sample. Serum potassium levels should be normal at the time of collection of blood sample. There is no indication of stopping any antihypertensive drugs except spironolactone and eplerenone which should be stopped for at least 6 weeks before case screening test. Practically, PA should be suspected if the PRA is suppressed (<1.0 ng/mL/h), PAC/PRA ratio is >30, and PAC concentration is above 15 ng/dL. A high PAC/PRA ratio is

a positive screening and not diagnostic test result and warrants confirmatory testing.

Confirmatory Tests

Various confirmatory tests are based on suppression of aldosterone secretion by salt loading. At the time of these tests, the subject should be normokalemic, should be on normal or high sodium intake diet, and should not be currently taking spironolactone or eplerenone for past 6 weeks. Many a times, vigorous replacement of potassium chloride is needed to maintain normokalemia. Various tests are oral salt loading test, IV saline loading test, and fludrocortisone loading test.

Oral salt loading test includes administration of 12.8 g of sodium chloride (5 g of sodium) for 3 consecutive days and then estimation of 24 h urinary aldosterone, sodium, and creatinine on the 3rd day of administration. It is important to document adequate sodium repletion, i.e. the 24-h urinary sodium excretion should exceed 200 mEq. If 24 h urinary aldosterone excretion exceeds 12 ug, the diagnosis of PA is confirmed. The sensitivity and specificity of the oral sodium loading test are 96% and 93%, respectively.

Intravenous Saline Infusion Test

Normal subjects show suppression of PAC after volume expansion with isotonic saline; subjects with PA do not show this suppression. The test is done after an overnight fast. 2 L of 0.9% sodium chloride solution is infused intravenously with an infusion pump over 4 h with the patient recumbent. Blood pressure and heart rate are monitored during the infusion. At the completion of the infusion, blood is drawn for the measurement of PAC. PAC levels in normal subjects decrease to <5 ng/dL, whereas most patients with PA do not suppress to <10 ng/dL. Post-infusion PAC values between 5 and 10 ng/dL are indeterminate and may be seen in patients with IHA.

Fludrocortisone Suppression Test

Fludrocortisone acetate is administered for 4 days (0.1 mg every 6 h) in combination with sodium chloride tablets (2 g 3 times daily with food). Blood pressure and serum potassium levels must be monitored daily. In the setting of low PRA, failure to suppress the upright 10 AM PAC to <6 ng/dL on day 4 is diagnostic of PA. Most centers no longer use this test.

Subtype Studies

The next step is distinguishing between APA and PAH from IHA and GRA. Unilateral adrenalectomy in patients with APA or PAH results in normalization of hypokalemia in all cases; hypertension is improved in all cases and is cured in 30–60%. In IHA and GRA, unilateral or bilateral adrenalectomy seldom corrects the hypertension, and hence, IHA and GRA should be treated medically. The delineation of these pathologies is done in following steps.

Computed Tomography (CT) of the Adrenal Glands

Contrast-enhanced CT (CECT) of adrenal gland with 2 mm slices is usually the first step. APAs are usually small hypodense adrenal nodules (<2 cm in diameter) on CT while in IHA adrenal glands may be normal on CT or may show nodular changes. Aldosterone-producing adrenal carcinomas are almost always larger than 4 cm in diameter and have an inhomogeneous phenotype. However, many a times, CT reveals normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macroadenomas. In these situations, additional testing is required to localize laterality or the source of excess aldosterone secretion.

If a solitary unilateral hypodense (HU <10) macroadenoma (>1 cm) and normal contralateral adrenal morphologic appearance are found on CT in a young patient (<35 years) with severe PA, unilateral adrenalectomy without further evaluation is a reasonable therapeutic option.

Small APAs are misdiagnosed as IHA on CT on the basis of normal-appearing adrenals. Furthermore, apparent adrenal microadenomas may actually represent areas of hyperplasia. Unilateral PAH may be visible on CT, or the PAH may appear normal on CT. Further, non-functioning unilateral adrenal micro- and macro-adenomas are not uncommon in subjects >40 years age. Adrenal CT is not accurate in distinguishing between APA and IHA. Adrenal venous sampling is currently the gold standard for defining unilateral from bilateral lesions and, hence, helps in taking the decision for surgical or medical treatment. In a systematic review of 38 studies including 950 patients with PA, adrenal CT/magnetic resonance imaging (MRI) results did not agree with the findings from AVS in 38% of subjects. 19% of these subjects could have been offered unnecessary surgery while another 19% could have been decline curative surgery.

Adrenal Venous Sampling

AVS is a highly specialized procedure requiring experienced intervention radiologist, center-specific protocol, appropriate patient selection, and meticulous data analysis. In expert hands, the AVS success rate is as high as 96%.[7]

Principally, the individual right and left adrenal are catheterized for sampling of blood for aldosterone and cortisol while the patient is maximally stimulated for cortisol secretion by synthetic ACTH stimulation. In addition, peripheral sample is collected form inferior vena cava at the level of external iliac vein for cortisol and aldosterone for peripheral concentration. The adrenal vein/IVC cortisol ratio is typically >10:1. Cortisol-corrected ratios (ratio of aldosterone and cortisol) are calculated from adrenal veins samples. A cutoff point of 4.0:1 for this ratio is used to indicate unilateral aldosterone excess while a ratio of <3.0:1 suggests bilateral aldosterone hypersecretion. AVS detection of unilateral aldosterone hypersecretion (APA or PAH) has 95% sensitivity and 100% specificity. At centers with experience with AVS, the complication rate is ≤2.5%. Complications include symptomatic groin hematoma, adrenal

hemorrhage, and dissection of an adrenal vein. Some centers and clinical practice guidelines recommend that AVS should be performed in all patients who have the diagnosis of PA. However, we perform AVS in all the cases with normal-appearing adrenals, adrenals with micronodularity, bilateral masses, and in subjects above the age of 35 years with unilateral hypodense, nodule >1 cm, and marked PA.

FH

GRA: FH Type I

GRA (FH Type I) is rare and is due to *CYP11B1/CYP11B2* chimeric gene and hyperaldosteronism is reversed with physiologic suppression with glucocorticoids. Mineralocorticoid production is regulated by ACTH instead of by the normal secretagogue, angiotensin II. GRA is characterized by early-onset hypertension that is usually severe and refractory to conventional antihypertensive therapies, aldosterone excess, suppressed PRA, and excess production of 18-hydroxycortisol and 18-oxycortisol.[8] Genetic testing is a sensitive and specific means of diagnosing GRA. Genetic testing for GRA should be considered for patients with PA who have a family history of PA, onset of PA at a young age (<20 years), or family history of strokes at a young age.

FH Type II

FH Type II is an autosomal dominant PA and does not suppress with dexamethasone, and GRA mutation testing is negative.[9] The molecular basis for FH type II is unclear.

FH Type III

FH Type III is due to a point mutation in and near the selectivity filter of the potassium channel KCNJ5. This KCNJ5 mutation produces increased sodium conductance and cell depolarization, triggering calcium entry into glomerulosa cells, the signal for aldosterone production, and cell proliferation.[10] Various germline mutations of KCNJ5 described are G151R and G151E. The patients have early-onset, mild PA and may have marked adrenal hyperplasia.

Somatic Mutations in *KCNJ5, ATP1A1, ATP2B3*, AND *CACNA1D* Genes

Somatic mutations of *KCNJ5* (G151R or L168R) have been identified in 34–47% of APAs. They are more prevalent in women and associated with higher pre-operative aldosterone levels but no significant surgical outcome.

Treatment of PA

The treatment goal in PA is to prevent the morbidity and fatality associated with hypertension, hypokalemia, and cardiovascular damage. Identifying the cause of PA is to help to determine the appropriate curative surgical or lifelong medical treatment.

Surgical Treatment of APA and Unilateral Hyperplasia

Unilateral laparoscopic adrenalectomy is currently the treatment for patients with APA or unilateral hyperplasia. Long-term cure of HTN in APA is 30–60%. Predictors for persistent hypertension are family history of hypertension, use of more than two antihypertensive drugs, old age, impaired renal functions, long duration of hypertension, and many a times are usually due to coexistent essential hypertension.

Pharmacologic Treatment

IHA and GRA should be treated medically. Spironolactone, the drug of choice, is initiated in dose of 12.5–25 mg/day initially and can be increased to 400 mg/day. Hypokalemia responds promptly while response to hypertension takes 4–8 weeks. The dose titration is adjusted according to serum potassium levels, to maintain it at high normal. After several months of therapy, the dosage of spironolactone often can be decreased to as little as 25–50 mg/day. Serum potassium and creatinine should be monitored frequently during the first 4–6 weeks of therapy (especially in patients with renal insufficiency or diabetes mellitus).

Eplerenone is a steroid-based antimineralocorticoid that acts as a competitive and selective MR antagonist. It is reasonable to start with a dose of 25 mg twice daily and titrated upward with maximum dose of 100 mg/day; the target is a high-normal serum potassium concentration without the aid of potassium supplements. In a randomized, double-blind trial comparing the efficacy, safety, and tolerability of eplerenone to that of spironolactone (100–300 mg vs. 75–225 mg, respectively) in patients with PA found spironolactone to be superior in terms of blood pressure lowering but to be associated with higher rates of male gynecomastia and female mastodynia.

Other Forms of Mineralocorticoid Excess or Effect

Endocrine hypertension associated with excess mineralocorticoid effect from DOC and cortisol should be considered if PAC and PRA are low in a patient with hypertension and hypokalemia.

Hyperdeoxycorticosteronism

Congenital Adrenal Hyperplasia

Deficiencies of 11β-hydroxylase (CYP11B1 and P450c11) or 17α-hydroxylase (CYP17 and P450c17) cause hypertension and hypokalemia because of hypersecretion of DOC.

11β-hydroxylase deficiency causes impaired conversion of DOC to corticosterone, high levels of DOC and 11-deoxycortisol; the substrate mass effect results in increased levels of adrenal androgens. It should be suspected in girls presenting in infancy or childhood with hypertension, hypokalemia, acne, hirsutism, and virilization. Boys present in early age onset hypertension, hypokalemia, and pseudoprecocious puberty.[11] The initial

screening tests include measurement of blood levels of DOC, 11-deoxycortisol, androstenedione, testosterone, and dehydroepiandrosterone sulfate (DHEAS): All of which should be increased above the upper limit of the respective reference ranges. Confirmatory testing includes germline mutation testing.

17A-hydroxylase Deficiency

17α-hydroxylase is essential for the synthesis of cortisol and gonadal hormones, and deficiency results in decreased the production of cortisol and sex steroid. Genetic 46, XY males present with either pseudohermaphroditism or as phenotypic females, and 46, XX females present with primary amenorrhea. Therefore, a person with this form of CAH may not come to medical attention until puberty. Children, adolescents, and young adults present with hypertension and spontaneous hypokalemia and low levels of aldosterone and renin.[12] The initial screening tests include measurement of serum androstenedione, testosterone, DHEAS, 17-hydroxyprogesterone, aldosterone, and cortisol: All of which should be either low or at the lower quartile of the respective references ranges. The plasma concentrations of DOC and corticosterone should be above the upper limit of the respective reference ranges. Confirmatory testing includes germline mutation testing.

DOC-producing Tumor

Pure DOC-producing adrenal tumors are very rare and usually large and malignant.[13] Some of these adrenal neoplasms cosecrete androgens and estrogens in addition to DOC, which may cause virilization in women or feminization in men. The typical clinical presentation would be that of relatively rapid onset of marked hypertension associated with hypokalemia and low blood levels of aldosterone and renin. A high level of plasma DOC or urinary tetrahydrodeoxycorticosterone and a large adrenal tumor seen on CT confirms the diagnosis.

Primary Cortisol Resistance

Increased cortisol secretion and plasma cortisol concentrations without evidence of Cushing syndrome are found in patients with primary cortisol resistance (or glucocorticoid resistance), a rare familial syndrome caused by genetic defects in the glucocorticoid receptor and the steroid-receptor complex.[14] The syndrome is characterized by hypokalemic alkalosis, hypertension, increased plasma concentrations of DOC, and increased adrenal androgen secretion. It usually presents in childhood with hypertension and spontaneous hypokalemia and low levels of aldosterone and renin. The initial screening tests include measurement of blood levels of cortisol, DOC, 11-deoxycortisol, androstenedione, testosterone, and DHEAS - all of which should be increased above the upper limit of the respective reference ranges. In addition, 24-h urinary cortisol excretion is above the upper limit of the reference range, and serum ACTH is not suppressed. Confirmatory testing includes germline mutation testing.

Apparent Mineralocorticoid Excess Syndrome

Apparent mineralocorticoid excess is the result of impaired activity of the microsomal enzyme HSD11B2, which normally inactivates cortisol in the kidney by converting it to the inactive compound, cortisone. Decreased HSD11B2 activity may be hereditary, or it may be secondary to pharmacologic inhibition of enzyme activity by glycyrrhizic acid, the active principle of licorice root (*Glycyrrhiza glabra*). Congenital apparent mineralocorticoid excess typically presents in childhood with hypertension, hypokalemia, low birth weight, failure to thrive, hypertension, polyuria and polydipsia, and poor growth.[15] Acquired apparent mineralocorticoid excess due to licorice root ingestion presents with hypertension and hypokalemia - the cause becomes evident when a good medical history is obtained. The diagnosis of apparent mineralocorticoid excess is confirmed by demonstration of an abnormal (high) ratio of cortisol-to-cortisone in a 24-h urine collection. The ratio of cortisol-to-cortisone is typically increased 10-fold above the normal value.

Liddle Syndrome

Liddle syndrome is caused by autosomal dominant mutations in the β- or γ-subunit of the amiloride-sensitive epithelial sodium channel resulting in enhanced activity of the epithelial sodium channel. It presents similar to PA with hypertension, hypokalemia, increased renal sodium reabsorption, and inappropriate kaliuresis but with low PRA and aldosterone levels.[16] It presents in children or young adults with hypertension and spontaneous hypokalemia and the presence of family history strongly supports the diagnosis. After exclusion of another diagnosis, a treatment trial with amiloride or triamterene should be considered. Liddle syndrome can easily be distinguished from apparent mineralocorticoid excess based on the good clinical response to amiloride or triamterene combined with a sodium-restricted diet, lack of efficacy of spironolactone and dexamethasone, and normal 24-h urine cortisone/cortisol ratio. Clinical genetic testing is available.

Pheochromocytoma

Catecholamine-secreting tumors from chromaffin cells of the adrenal medulla and the sympathetic ganglia are called as pheochromocytomas and catecholamine-secreting paragangliomas, respectively. The prevalence of pheochromocytoma has been estimated at 0.1–0.6% in subjects attending tertiary care centers for hypertension. It is important to suspect, confirm, localize, and resect these tumors because (1) the associated hypertension is curable with surgical removal of the tumor, (2) a risk of lethal paroxysm exists, (3) at least 10% of the tumors are malignant, and (4) 40% of these tumors are familial and their detection in the proband may result in early diagnosis in other family members.

Clinical Presentation

Pheochromocytoma presents with equal frequency in both males and females, usually in 3–5th decade. Classically, they present with sustained or paroxysmal hypertension or a combination of both. Typically, the paroxysm presents as episodic palpitation, pallor, tremor, headache, and diaphoresis, the symptoms complex usually lasting for <30 min.[17] Paroxysms are either spontaneous or can be precipitated by postural change, anxiety, medications (e.g. β-adrenergic antagonists, metoclopramide, and anesthetic agents), exercise, or maneuvers that increase intra-abdominal pressure. Additional clinical signs of pheochromocytoma include hypertensive retinopathy, cardiomyopathy, orthostatic hypotension, angina, nausea, constipation, megacolon, hyperglycemia, diabetes mellitus, hypercalcemia, Raynaud phenomenon, livedo reticularis, erythrocytosis, painless hematuria, and mass effects from the tumor. Rarely, pheochromocytoma can present as sudden hypotension or can be simply asymptomatic. With increasing the use of imaging, nowadays, 50% of adrenal pheochromocytoma are discovered as incidentaloma on imaging.

Syndromic Forms of Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma can occur in isolation or as a part of inherited syndrome complex. Since 1990, 16 pheochromocytoma/paraganglioma susceptibility genes have been reported: *NF1*, *RET*, *VHL*, *SDHD*, *SDHC*, *SDHB*, *EGLN1 (PHD2)*, *EGLN2* (*PDH1*), *KIF1B*, *SDHAF2*, *IDH1*, *TMEM127*, *SDHA*, *MAX*, *HIF2A*, and *FH*.[18] Various syndromes associated with pheochromocytoma are multiple endocrine neoplasia (MEN) 2A (primary hyperparathyroidism, medullary thyroid carcinoma, pheochromocytoma, cutaneous lichen amyloidosis, very rarely Hirschsprung disease), MEN 2b (pheochromocytoma, mucocutaneous neuromas, marfanoid habitus, myelinated corneal nerves, and intestinal ganglioneuromas), von Hippel-Lindau disease (pheochromocytoma or paraganglioma, hemangioblastoma involving the cerebellum, spinal cord, or brainstem, retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors, endolymphatic sac tumors of the middle ear, serous cystadenomas of the pancreas, and papillary cystadenomas of the epididymis and broad ligament), neurofibromatosis 1 (NF1, neurofibromas, multiple café au lait spots, axillary and inguinal freckling, iris hamartomas [Lisch nodules], bony abnormalities, central nervous system gliomas, macrocephaly, and cognitive deficits), and Carney triad or syndrome (gastrointestinal stromal tumor, pulmonary chondroma, catecholamine-secreting paraganglioma, esophageal leiomyoma, and adrenal adenoma). Most cases of familial paraganglioma are caused by mutations in the succinate dehydrogenase subunit genes (*SDHB*, *SDHC*, *SDHD*, *SHDA*, and *SDHAF2*), which make up portions of mitochondrial complex II. As of 2014, a total of 403 different germline mutations in the *SDH* genes associated with pheochromocytoma/paraganglioma were reported in the literature; 62.52% in *SDHB*, 35% in *SDHD*, 10% in *SDHC*, 2% in *SDHA*, and 1% in *SDHAF2*. 78 mutations were found in malignant tumors: 76% in SDHB, 19% in SDHD, and 5% in SDHC. In addition, sporadic pheochromocytoma (unilateral adrenal tumor with negative family history), 2% have *TMEM127* mutations. *MAX* germline mutations and germline mutations in the *FH* gene encoding fumarate hydratase have been seen in sporadic pheochromocytoma. In view of variety of mutation, genetic testing has been advocated in following situations: Genetic testing should be considered if a patient has one or more of the following: (1) Paraganglioma, (2) bilateral adrenal pheochromocytoma, (3) unilateral adrenal pheochromocytoma and a family history of pheochromocytoma/paraganglioma, (4) unilateral adrenal pheochromocytoma with onset at a young age (<45 years), or (5) other clinical findings suggestive of one of the previously discussed syndromic disorders. A sequential genetic testing algorithm, based on biochemical phenotype, age, and tumor, has been proposed. However, next-generation sequencing now being widely available and more cost-effective, it is now proposed to be more helpful.

Diagnostic Investigation

Clinical

Pheochromocytoma should be suspected in patients who have one or more of the following: Hyperadrenergic spells, resistant hypertension, a familial syndrome that predisposes to catecholamine-secreting tumors (e.g. MEN2, NF1, VHL, and Carney triad), family history of pheochromocytoma, an incidentally discovered adrenal mass with imaging characteristics consistent with pheochromocytoma, pressor response during anesthesia, surgery, or angiography, onset of hypertension at a young age (<20 years), and idiopathic dilated cardiomyopathy.

Biochemical

The diagnosis must be confirmed biochemically by the presence of increased concentrations of fractionated metanephrines and catecholamines in urine or plasma.[19] Most laboratories now measure fractionated catecholamines (dopamine, norepinephrine, and epinephrine) and fractionated metanephrines (metanephrine and normetanephrine) by high-performance liquid chromatography with electrochemical detection or tandem mass spectrometry. Measurements of fractionated metanephrines and catecholamines in a 24-h urine collection have high sensitivity (98%) and specificity (98%). In addition, measurement of plasma fractionated metanephrines is a good first-line test for children, because obtaining a complete 24-h urine collection is difficult in pediatric patients. In normotensive laboratory volunteers, the 95th percentiles are 428 μg for normetanephrine and 200 μg for metanephrine. Usually, the values are 2–3 times of normal range in subjects with pheochromocytoma. The 24-h urinary VMA excretion has poor diagnostic sensitivity and specificity compared with fractionated 24-h urinary metanephrine. Certain drugs (e.g. tricyclic antidepressants, antipsychotics, beta-blockers, centrally acting α2-adrenergic receptor agonist-

like clonidine, etc.,) and clinical situations (acute stress/illness, e.g. stroke, myocardial infarction, congestive heart failure, and obstructive sleep apnea) should be avoided during the collection of urine or plasma collections. Chromogranin A is not specific for pheochromocytoma, and is, in fact, a marker of neuroendocrine tumor.

Localization

Localization studies for pheochromocytoma must be initiated only after biochemical confirmation. CECT or spin echo MRI of the abdomen and pelvis is the initial imaging with sensitivity of >95% and specificity of >65%. Pheochromocytoma has contrast enhancement with intravenous. High signal intensity on T2-weighted MRI, cystic and hemorrhagic changes, and variable size.[20] The tumor may be bilateral approximately 85% of these tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis. The most common locations of catecholamine-secreting paragangliomas include superior abdominal para-aortic region, 46%; inferior abdominal para-aortic region, 29%; urinary bladder, 10%; mediastinum, 10%; head and neck, 3%; and pelvis, 2%.

^{123}I-MIBG scintigraphy is indicated when CT or MRI is negative. This radionuclide accumulates preferentially in catecholamine-producing tumors. The sensitivity and specificity are 80% and 99%, respectively. AVS for catecholamines is misleading and, hence, not advised.

Treatment

Complete surgical resection, either laparoscopic or open laparotomy, is indicated in all the subjects with pheochromocytoma and the success rates are 98–100% with cures of hypertension. Pre-operative preparation with alpha blockers (prazosin, terazosin, doxazosin, and phenoxybenzamine) and fluid and salt replacement for 7–14 days is crucial for smooth perioperative hemodynamic stability.[21] Adequate blockade of catecholamine effect is achieved when target blood pressure is <120/80 mmHg in the seated position, with systolic blood pressure >90 mmHg (standing), and absence of paroxysms and postural hypotension. The β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective with target to achieve heart rate 60–80/min. Metyrosine inhibits catecholamine synthesis by blocking the enzyme tyrosine hydroxylase and is used in inoperable metastatic pheochromocytoma. Calcium channel blocker, especially nicardipine, which blocks norepinephrine-mediated calcium transport into vascular smooth muscle, has been used successfully at several centers. Approximately 1–2 weeks after surgery, 24-h urinary fractionated catecholamines and metanephrines should be measured. If the levels are normal, the resection of the pheochromocytoma should be considered complete. The survival rate after removal of a benign pheochromocytoma is almost equal to that of age- and sex-matched normal control subjects.

Other Endocrine Disorders Associated with Hypertension

Cushing Syndrome

Hypertension occurs in 75–80% of patients with Cushing syndrome.[22] The mechanisms of hypertension include increased production of DOC, enhanced pressor sensitivity to endogenous vasoconstrictors (e.g. epinephrine and angiotensin II), increased cardiac output, activation of the RAA system by increased hepatic production of angiotensinogen, and cortisol activation of the MR. Diagnosis is established by demonstration of lack of suppression of cortisol on overnight dexamethasone suppression, and low-dose dexamethasone suppression, elevated midnight salivary cortisol, and 24-h urinary cortisol excretion, along with serum ACTH estimation.

Thyroid Dysfunction

Hyperthyroidism

Thyrotoxic patients usually have tachycardia, high cardiac output, increased stroke volume, decreased peripheral vascular resistance, and increased systolic blood pressure.[23] The hypertension is due to enhanced catecholamine sensitivity due to excess thyroid hormones. Treatment is etiology specific and beta-blockers.

Hypothyroidism

Hypertension is usually diastolic and is due to increased systemic vascular resistance and extracellular volume expansion.[24] Thyroxine replacement decreases blood pressure in most patients with hypertension and normalizes blood pressure in one-third of them.

Hypercalcemia and Primary Hyperparathyroidism

Hypertension is observed in 10–60% of subjects with primary hyperparathyroidism.[25] The pathogenesis is still unclear. Hypertension may or may not remit after successful parathyroidectomy.

Acromegaly

Hypertension occurs in 20–40% of the patients with acromegaly[26] and is associated with sodium retention and extracellular volume expansion and its remits after cure of hypersomatotropism.

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