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Endocrine Hypertension: A Practical Approach

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Abstract

Elevated blood pressure resulting from few endocrine disorders (endocrine hypertension) accounts for a high proportion of cases of secondary hypertension. Although some features may be suggestive, many cases of endocrine hypertension remain silent until worked up for the disease. A majority of cases result from primary aldosteronism. Other conditions that can cause endocrine hypertension are: congenital adrenal hyperplasia, Liddle syndrome, pheochromocytomas, Cushing's syndrome, acromegaly, thyroid diseases, primary hyperparathyroidism and iatrogenic hormone manipulation. Early identification and treatment of the cause of endocrine hypertension may help to reduce morbidity and mortality related to these disorders. This article gives a comprehensive and practical approach to the diagnosis and management of endocrine hypertension.

Keywords

Endocrine hypertension • Primary aldosteronism • Congenital adrenal hyperplasia • Liddle syndrome • Pheochromocytoma • Cushing's syndrome • Acromegaly • Thyroid disease • Primary hyperparathyroidism

1 Introduction

Hypertension is a chronic condition with multisystem involvement and is associated with high morbidity and mortality. The prevalence of hypertension is approximately 40 % among adults over the age of 25 years and contributes to 45–50 % of deaths due to heart disease and stroke (World Health Organization. Obesity and overweight 2015). Although the prevalence of hypertension is high in the general population, only in around 10 % of cases an underlying specific cause can be identified (secondary hypertension), of which the majority are related to renal and endocrine disorders (Young 2015). If secondary hypertension is suspected, it is important

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to identify the cause, as treatment of the primary condition may lead to complete or partial cure of hypertension.

A multitude of endocrine disorders can present with secondary hypertension, collectively termed here as endocrine hypertension. Some of these disorders may present with unique clinical features while the others may be asymptomatic and identified during work-up of resistant hypertension (refractory to standard anti-hypertensive therapy), or a hypertension-related complication. Early diagnosis and appropriate management of the primary illness often result in marked improvement or cure of hypertension. In this chapter, we describe a comprehensive and practical approach to endocrine hypertension.

2 When to Suspect Endocrine Hypertension?

Secondary hypertension is suspected in patients who present with: hypertension at an early age, sudden onset of uncontrolled hypertension, loss of control over previously well-controlled blood pressure and a hypertensive emergency (Velasco and Vongpatanasin 2014; Weber et al. 2014; Thomas et al. 2015).

Endocrine hypertension is the second most common cause of secondary hypertension after renal disease, and forms a major aetiological factor for resistant hypertension. A diagnosis of endocrine hypertension may be obvious when patients present with typical clinical features of the underlying condition like acromegaly, Cushing syndrome, hyperthyroidism, hypothyroidism and features of virilisation in congenital adrenal hyperplasia (Young 2015). They may present with a typical history e.g. paroxysmal palpitations and orthostatic hypotension in phaeochromocytoma (Pappachan et al. 2014; Desai et al. 2009; Kiernan and Solórzano 2016). Occasionally routine laboratory tests in a patient with hypertension may raise the suspicion of an endocrine cause e.g. hypokalemia in mineralcorticoid excess (Thomas et al. 2015). However, in a high proportion of patients, an endocrine cause may not be obvious, and all patients suspected to have secondary hypertension should be evaluated for an endocrine cause unless an alternative aetiology for hypertension is obvious from the initial clinical and laboratory picture.

3 Causes of Endocrine Hypertension

A number of endocrine conditions can result in hypertension although only a few of them are common in clinical practice. A detailed discussion of individual disorders, the clinic-pathological features and diagnostic evaluation is elaborated below.

4 Primary Mineralocorticoid Excess

Mineralocorticoids are steroid hormones that control the water and salt balance in the body. Aldosterone is the principal endogenous mineralocorticoid hormone in the body although other hormones including glucocorticoids and sex steroids may exert mineralocorticoid effects. Aldosterone is synthesised by the zona glomerulosa cells of the adrenal cortex, and is under control of angiotensin II, plasma potassium levels, and to a lesser extent adrenocorticotrophin (ACTH).

Clinical conditions in which primary mineralocorticoid excess can occur are: overproduction of mineralocorticoid hormones as in primary aldosteronism (PA) and congenital adrenal hyperplasia (CAH), or increased effect of mineralocorticoid hormones as in Liddle syndrome, syndrome of apparent mineralocorticoid excess (AME), pseudohypoaldosteronism type 2 (Gordon syndrome) and Geller syndrome. These conditions are elaborated in the sections below.

4.1 Hypermineralocorticoidism

Overproduction of aldosterone occurs in PA or CAH, and these disorders are elaborated in the following sections.

4.1.1 Primary Aldosteronism (PA)

PA is one of the most common disorders that causes secondary hypertension and forms the majority of cases of endocrine hypertension. The disease accounts for 5–13 % of cases in people with age of onset of hypertension between 30 and 60 years (Thomas et al. 2015; Young 2007). About 10 % of cases in hypertension clinics, 4 % in the community (Hannemann and Wallaschofski 2012; Boulkroun et al. 2015), and nearly 20 % with resistant hypertension are estimated to be resulting from PA (Boulkroun et al. 2015). The variability in the reported incidence is related to the use of different definitions, biochemical tests and cut-offs. Nearly 60–65 % of cases of PA are from idiopathic hyperaldosteronism (IHA) and 30–35 % result from an aldosterone producing adrenal adenoma (APA) (Thomas et al. 2015; Young 2007). Roughly 5 % of cases of PA are familial (familial hyperaldosteronism type I, II and III [FH-I, II and III]) with clear genetic background (Zennaro et al. 2015a).

Pathophysiology

PA results from aldosterone over-production with a consequent suppression of plasma renin, and manifests with hypertension, retention of sodium, and over-excretion of potassium that may lead to hypokalemia (Funder et al. 2008). Although many of the complex molecular, cellular and genetic mechanisms involved in these pathways have been recently elucidated (Boulkroun et al. 2015; Zennaro et al. 2015a; Piaditis et al. 2015), they are beyond the scope of this chapter. Excess production of aldosterone in PA has multiple biologic and pleiotropic effects in human body that results in the manifestations and complications of the disease.

Aldosterone causes retention of sodium from the distal renal tubules and collecting ducts in exchange for hydrogen and potassium ions. The corresponding increase in the water absorption results in an increase in blood volume and blood pressure and the loss of hydrogen ions and potassium results in a state of hypokalemic metabolic alkalosis in some but not all patients (Thomas et al. 2015; Mulatero et al. 2004). A reduction of plasma renin levels is classical of PA. Apart from the usual complications related to essential hypertension, PA is found to be associated with elevated risk of cardiac hypertrophy and fibrosis, vascular endothelial dysfunction, albuminuria and nephrocalcinosis.

Clinical Presentation

Although the classical presentation of PA is with resistant hypertension and hypokalemia (sometimes symptomatic), it is not often observed in clinical practice (Thomas et al. 2015; Funder et al. 2008). The following categories of cases should be considered for screening: hypertension inadequately controlled with three or more antihypertensive medications, hypertension with an adrenal incidentaloma, hypertension in young adults, or those presumed to have secondary hypertension (Thomas et al. 2015; Young 2007). Apart from these categories, the 2008 American Endocrine Society Guidelines also suggest screening for: hypertensives with diuretic-induced hypokalemia, patients with family history of early-onset hypertension or stroke before 40 years of age and hypertensive patients with a first degree relative having PA (Thomas et al. 2015; Manolopoulou et al. 2015).

Diagnostic Approach

Initial Screening Patients with suspected PA should be tested with an estimation of plasma aldosterone and renin levels with the calculation of aldosterone to renin ratio (ARR). The assay should be ideally performed in the morning after the individual has been out of bed for 2 h and seated for 5–15 min (Thomas et al. 2015; Funder et al. 2008). Different laboratories use different units and cut off values for ARR depending on the assay, and a practical approach could be following the local guidelines. A recent study using a method-specific ARR cut-off of 1.2

(ng/dl)/(μIU/ml), determined with direct, automated chemi-luminescence immunoassays allowing the simultaneous measurement of plasma aldosterone and renin concentrations, provided 98.9 % sensitivity and 78.9 % specificity (Manolopoulou et al. 2015). These results have been reproduced by other studies but method-specific cut off needs to be derived. Different centres use renin activity or renin concentration, and the ratio cut-off is significantly affected by this and other laboratory-based variables. An absolute cut-off value for aldosterone concentration (also method-specific) is often used as an additional criterion to make ARR more specific. Aldosterone antagonists and beta-blockers should be withdrawn prior to the test as they disproportionately affect the ARR.

Confounders Several antihypertensive medications can interfere with the screening results to a varying extent because of interference with the renin-angiotensin-aldosterone (RAA) system causing high false-positive and false-negative rates, with betablockers and diuretics being the main culprits. Hypokalemia, and treatment with antihypertensive medications such as dihydropyridine group of calcium channel blockers, angiotensin convertase enzyme inhibitors and angiotensin II receptor blockers, can cause false negative results of ARR in patients with mild PA. Discontinuation of interfering medications for sufficient time period may be considered if feasible. For example, diuretics and aldosterone antagonists should be withdrawn 4 weeks prior to, and the other antihypertensives described above, 2 weeks prior to the intended ARR estimation (Funder et al. 2008). Antihypertensives such as verapamil (slow release), hydralazine and alpha-adrenergic blockers possess minimal effects on RAA system and are recommended for control of hypertension before ARR measurement if other antihypertensive drugs are to be discontinued (Thomas et al. 2015; Funder et al. 2008). However, in patients with severe hypertension resistant to conventional medications, switching to these drugs may not be easy, considering the anticipated hypertensive complications.

Biochemical Confirmation Although a raised ARR in a clinically relevant scenario is highly suggestive of PA, one of the four confirmatory tests is recommended by the American Endocrine Society Guidelines (Funder et al. 2008). These tests are: oral sodium loading with measurement of urinary aldosterone excretion, intravenous saline infusion with measurement of plasma aldosterone levels (levels suppressed in absence of PA), fludorcortisone suppression test and captopril challenge test. The latter two tests are not routinely used now, and severe uncontrolled hypertension and heart failure are relative contraindications to the former two (Thomas et al. 2015). The former two confirmatory tests may become necessary in cases with mild PA, where the ARR is only marginally elevated in the absence of severe hypertension or heart failure. A detailed description and interpretation of the confirmatory tests and results are beyond the scope of this chapter and are freely available to the readers in the full text of the American Endocrine Society Guidelines (Funder et al. 2008).

Adrenal Imaging Computed tomography (CT) scan of the adrenal glands is recommended in all cases of PA for localisation of the disease and to exclude the small possibility of an adrenocortical carcinoma (Thomas et al. 2015; Funder et al. 2008). Adrenal CT is preferred over magnetic resonance imaging (MRI) as an imaging modality for localisation purpose because it is more economical and has better spatial resolution. However, adrenal imaging had a low sensitivity of 58.6 % to detect unilateral disease (Lim et al. 2014).

Adrenal Venous Sampling (AVS) AVS is the gold standard test for detection of the source of aldosterone excess, and is recommended in most cases for lateralisation of the abnormal adrenal gland if a surgical cure is contemplated. The technical difficulty with the procedure, lack of availability in many centres and relatively higher complication rates (about 5 %) are the main concerns in the routine performance of AVS. A recent expert consensus statement recommends avoiding AVS in the following situations: age

is < 40 years with marked PA in presence of a typical unilateral adrenal adenoma and normal appearance of the opposite adrenal on CT, suspicion of adrenocortical carcinoma from adrenal imaging, high risk cases for adrenalectomy, proven cases of FH-I and FH-III (Thomas et al. 2015; Rossi et al. 2014).

Tests for Familial Hyperaldosteronism (FH) FH-I (GRA) is screened by a low-dose dexamethasone suppression test with serial measurements of blood pressure and plasma aldosterone levels (Mussa et al. 2012; Korah and Scholl 2015). Normalisation of blood pressure and suppression of aldosterone are characteristics of FH-I. In addition, urinary 18-oxocortisol and 18-hydroxycortisol are usually elevated in patients with FH-I (Mussa et al. 2012). In patients with FH-II, blood pressure is un-responsive to glucocorticoid challenge and aldosterone suppression is partial or absent (Mussa et al. 2012). Urinary 18-oxocortisol and 18-hydroxycortisol levels are normal/moderately elevated. Blood pressure is unresponsive/increases with a paradoxical increase in aldosterone levels occurs in cases of FH-III during dexamethasone suppression test (Mussa et al. 2012). The urinary 18-steroid metabolites are very high in FH-III. Genetic testing confirms the autosomal dominant gene mutations in all the three forms of FH (Korah and Scholl 2015; Zennaro et al. 2013).

Management of PA

Surgical Management Surgical management is possible only in selected cases of PA where there is a clear evidence of lateralisation of the aldosterone excess to the side of an adrenal adenoma as described above. A recent systematic review showed that adrenalectomy for unilateral disease was associated with normalization of blood pressure in about 42 % (range 20–72) and cure of PA in 96–100 % with a mean complication rate of 4.7 % among 1056 patients (Muth et al. 2015). Compared to medical therapy, use of fewer antihypertensive drugs, improvement of quality of life, and possibly all-cause mortality were observed after surgery, although without an observed benefit on cardiovascular complications.

Laparoscopic adrenalectomy is the preferred surgical procedure because of lower morbidity, shorter length of hospital stay and faster recovery compared to open adrenalectomy. Partial adrenalectomy may be an option in selected case of unilateral PA. Both hypertension and hypokalemia should be well controlled pre-operatively, and levels of plasma aldosterone and renin should be measured postoperatively to assess the biochemical response (Thomas et al. 2015; Funder et al. 2008). Withdrawal of potassium supplements and mineralocorticoid receptor (MR) antagonist are usually possible on the first postoperative day after successful surgery, with reduction/discontinuation of antihypertensive medications within 1–6 months in most cases. Bilateral adrenalectomy may be necessary in FH-III to control the disease (Mussa et al. 2012).

Medical Therapy Medical treatment is the option in a majority of cases of PA with bilateral disease and in cases not appropriate for adrenalectomy. MR antagonist spironolactone is the first line of treatment. With a starting dose of 12.5–25 mg, the dose is gradually up-titrated to optimise the dose (usually up to 100 mg daily) to get adequate control of BP and potassium levels. Eplerenone, a selective MR antagonist, is started at a dose of 25 mg once or twice daily. Caution must be taken in chronic kidney disease stage 3 and above while using these drugs. Amiloride/triamterene are useful alternative medications if MR antagonists are not tolerated/contra-indicated (Funder et al. 2008).

PA resulting from FH-I (GRA) should be managed with glucocorticoids in adults and MR antagonists in paediatric cases (because of the effect of steroids on growth retardation) until they reach adulthood. Starting dose of dexamethasone is 0.125–0.25 mg or prednisolone is 2.5–5 mg at night and the doses are titrated to partially suppress the ACTH levels to optimise the aldosterone levels and BP control (Funder

et al. 2008). FH-II is managed with MR antagonists +/− amiloride to optimise BP control.

4.1.2 Congenital Adrenal Hyperplasia (CAH) with Mineralocorticoid Excess

CAH is the most common inborn error of adrenal gland function (Speiser 2015; Sahakitrungruang 2015; Miller and Auchus 2011). There are different forms of CAH depending on the type of genetic mutations and the related enzyme defect in the adrenocortical hormone synthesis that cause these disorders. Two types of enzyme defects cause mineralocorticoid excess in CAH, viz. 11-β-hydroxylase deficiency (11OHD) and 17-α-hydroxylase deficiency (Sahakitrungruang 2015).

About 5–8 % of cases of CAH among Caucasians and about 15 % among Middle-Eastern populations results from 11OHD (Sahakitrungruang 2015; Miller and Auchus 2011). The enzyme deficiency causes decreased cortisol production with accumulation of 11-deoxycortisol and 11-deoxycorticosterone (DOC; a mineralocorticoid precursor). The disease is transmitted as an autosomal recessive trait with more than 80 mutations described already (Zennaro et al. 2015b). Hypertension and varying degrees of virilisation and precocious puberty in both sexes are the results of 11OHD clinically.

17-α-hydroxylase deficiency results in a reduction of cortisol synthesis with overproduction of corticosterone, and deoxycorticosterone (mineralocorticoid). Hypertension, hypokalemia and sexual infantilism secondary to hypergonadotropic hypogonadism are the common clinical features of this disorder. Inheritance pattern is autosomal recessive with more than 90 gene mutations described to date (Zennaro et al. 2015b).

Diagnostic Approach to CAH (with Mineralocorticoid-Induced Hypertension)

Diagnosis of 11OHD is established by elevated baseline levels of DOC and 11-deoxycortisol with significant increase in the levels following ACTH challenge (Sahakitrungruang 2015; Zennaro et al. 2015b). Plasma renin and aldosterone levels will be low. Definitive diagnosis is proved with genetic testing for the mutation. 17-α-hydroxylase deficiency results in elevated levels of DOC, ACTH and gonadotropins with suppressed levels of androgens and estrogen (Zennaro et al. 2015b; Kim and Rhee 2015). Unlike the classical and non-classical forms of CAH, levels of 17-hydroxyprogesterone levels are low and the levels do not rise with ACTH challenge. Genetic testing establishes the diagnosis with identification of the related mutations.

Management

The mainstay of management in patients with 11OHD is glucocorticoids that normalise ACTH, the driving force for DOC overproduction, with improvement of hypertension (Zennaro et al. 2015b). Addition of MR antagonists such as spironolactone or eplerenone may be necessary in some cases to treat hypertension. Patients with 17-α-hydroxylase deficiency should be treated with glucocorticoids and sex steroids when necessary (Zennaro et al. 2015b; Kim and Rhee 2015). The genital abnormalities related to virilisation should be managed by appropriate surgical procedures.

Increased Mineralocortocoid Action

Even with normal levels of mineralocorticoid hormones, mineralocorticoid-related hypertension can result from rare genetic disorders from exaggerated actions of the hormone at the receptor/effecter-tissue levels. These disorders are briefly discussed in the following section.

4.1.3 Liddle Syndrome

This is an autosomal dominant genetic disorder associated with hypertension, hypokalemia, metabolic alkalosis, and low plasma renin and aldosterone levels. Because of similarity to the clinical presentation of PA, the condition is termed "pseudoaldosteronism" (Wang et al. 2015). Liddle syndrome results from gain-of-function mutations in genes encoding the subunits of epithelial sodium channel (ENaC) that cause increased sodium re-absorption and potassium loss from the kidney and hypertension

(Zennaro et al. 2015b; Wang et al. 2015; Melcescu et al. 2012).

Diagnosis is considered in hypertensives with a family history of early-onset hypertension, hypokalemia, low levels of renin and aldosterone, and prompt response to ENaC antagonists such as amiolride and triamterine without response to MR antagonists (Zennaro et al. 2015b; Wang et al. 2015; Melcescu et al. 2012). Confirmation of the diagnosis is by screening for mutations in the genes encoding the β and γ subunits ENaC. Patients are managed by a low sodium diet and ENaC antagonists.

4.1.4 Syndrome of Apparent Mineralocorticoid Excess (AME)

AME is an autosomal recessive disorder characterised by hypertension, hypokalemia, metabolic alkalosis with low levels of plasma renin and aldosterone levels (Zennaro et al. 2015b; Melcescu et al. 2012). It is caused by mutations in the HSD11B2 gene coding for the enzyme 11β-Hydroxysteroid dehydrogenase 2 (HSD11B2) on chromosome 16 (Zennaro et al. 2015b; Melcescu et al. 2012). This enzyme is responsible for the inter-conversion of cortisol to cortisone in aldosterone-selective tissues including kidneys liver, colon, salivary glands, lungs, placenta and some neural tissues. Around 40 different types of mutations are described in the gene already (Zennaro et al. 2015b).

Severe form of the disease is usually diagnosed in early childhood with hypertension, polyuria, polydypsia, hypokalemia, metabolic alkalosis and failure to thrive in presence of suppressed plasma renin and aldosterone levels (Zennaro et al. 2015b; Melcescu et al. 2012). Short stature, renal cysts and nephrocalcinosis may be present in some cases (Zennaro et al. 2015b; New et al. 2005). Milder forms may present during adult life. Biochemical diagnosis of AME is based on measurement of the ratio of urinary metabolites of cortisol to cortisone (high ratio in cases) (Zennaro et al. 2015b; New et al. 2005). Confirmation of the diagnosis is by genetic testing. Management is usually by MR antagonists +/− thiazide diuretics along with small doses of dexamethasone.

4.1.5 Pseudohypoaldosteronism Type 2 (Gordon Syndrome; Familial Hyperkalemic Hypertension)

This is a rare genetic disorder associated with hypertension, hyperkalemic-hyperchloremic metabolic acidosis, low renin and normal or elevated levels of aldosterone (Zennaro et al. 2015b; Melcescu et al. 2012). Multiple genetic mutations are identified (in the genes WNK1, WNK4, KLHL3 and CUL3) that modulate the thiazide-sensitive Na-Cl cotransporter in the kidney leading to increased re-absorption of sodium and chloride from the kidney with the resultant biochemical and clinical manifestations of the disease.

Diagnosis is based on the biochemical abnormalities described above and the genetic testing for different culprit gene mutations (Zennaro et al. 2015b; Melcescu et al. 2012). Management of the disease is with dietary sodium restriction and thiazide diuretics.

4.1.6 Geller Syndrome

This disorder results from a mutation activating the mineralocorticoid receptor (MR) that was first described by Geller et al. in 2000 (Geller et al. 2000). The index case presented with early-onset severe hypertension associated with low plasma renin and aldostereone, and exacerbation of hypertension during pregnancy. So far, only one family has been identified with a p. Ser810Leu mutation, located in the ligand binding domain of the MR (Zennaro et al. 2015b; Melcescu et al. 2012). Amiloride may be effective in the correction of the biochemical abnormalities and improvement of hypertension, but spironolactone has to be avoided as it is a potent agonist of the mutant receptor (Zennaro et al. 2015b).

A flow chart depicting the algorithm for work up and management of primary mineralocorticoid excess states is shown in Fig. 1.

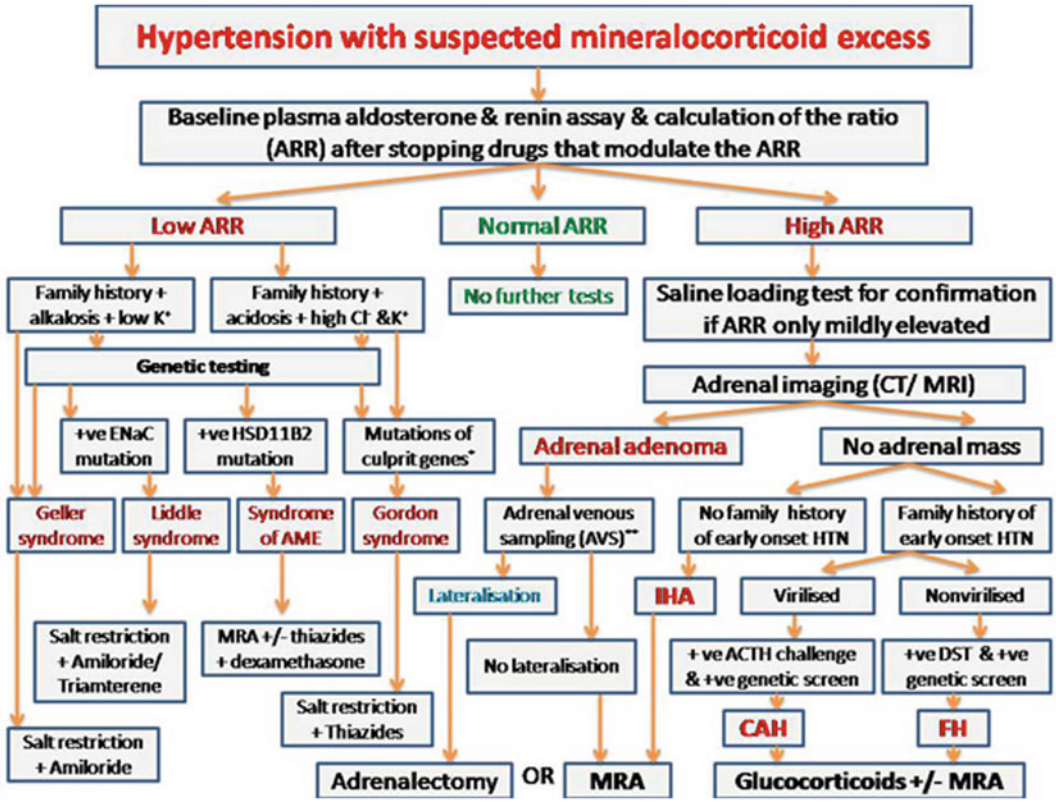

Fig. 1 An algorithm for diagnostic evaluation and management of primary mineralocorticoid excess states (*HTN* hypertension, *CT* computed tomography, *MRI* magnetic resonance imaging, K^+ potassium, Cl^- chloride, *ENaC* epithelial sodium channel, *HSD11B2* 11β-Hydroxysteroid dehydrogenase 2, *AME* apparent mineralocorticoid excess, *IHA* idiopathic hyperaldosteronism, *MRA* mineralocorticoid antagonist, *ACTH* Adrenocorticotropic hormone, *DST* dexamethasone suppression test, *CAH* congenital adrenal hyperplasia, *FH* familial hyperaldosteronism, *Culprit genes** WNK1, WNK4, KLHL3 and CUL3, *(AVS)*** adrenal venous sampling may be avoided in certain situations as mentioned in the text)

5 Pheochromocytomas and Paragangliomas

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare neuroendocrine tumours arising from the chromaffin tissues of the embryonic neural crest cells that become the adrenal medulla and autonomic neural ganglia in adult life. With an estimated annual incidence of 2–8 per million, these tumors account for 0.2–0.6 % of hypertension in the community (Pappachan et al. 2014; Kasperlik-Zaluska et al. 2006). About 85 % of pheochromocytomas arise from the adrenal medulla (PCCs) and the remainder from the extra-adrenal autonomic ganglia (PGLs).

Pathophysiology

Increased production and release of catecholamines (epinephrine, norepinephrine and dopamine) by the tomors to circulation result in the clinico-pathological manifestations of PCCs and PGLs. Catecholamines cause intense vasospasm and hypertension through α-adrenergic effect, and vasodilatation, diaphoresis and tachycardia from the β-adrenergic effect (Pappachan et al. 2014). Severe orthostatic hypotension with syncopal episodes can occasionally result from unbalanced effects of α-

and β-adrenergic receptors in different vasculature in the body (Pappachan et al. 2014; Desai et al. 2009).

The paroxysmal nature of the catecholamine release may explain the episodic nature of symptoms in PCCs/PGLs. Recurrent surge of these hormones may cause a (reversible) form of cardiomyopathy called catecholaminergic cardiomyopathy (Pappachan et al. 2014; Desai et al. 2009). 10–15 % of PCCs and 20–50 % of PGLs can be malignant, and as there is no clear-cut histological criteria to determine malignancy in resected tumors, life-long follow up for recurrence in an appropriate clinical scenario is recommended by many authorities (Parenti et al. 2012; Tsirlin et al. 2014; Lenders et al. 2014). Several genetic mutations have been recently described in PCCs/PGLs (Pappachan et al. 2014) that may be associated with malignant potential and inheritance to successive generations, and the recent endocrine society guidelines in 2014 recommend appropriate testing and follow up algorithm of the disease (Lenders et al. 2014).

Clinical Features

Although the classical clinical presentation is with headaches, palpitations and sweating with hypertension, many of these tumours present with protean manifestations including prolonged periods of clinical silence. <1 % of resistant hypertension cases are related to PCCs/PGLs (Rimoldi et al. 2014). With the increasing use of cross sectional abdominal imaging for medical diagnostics, many cases of PCCs/PGLs are diagnosed in the recent years while evaluating adrenal incidentalomas. About 4 % of adrenal incidentalomas are reported to be PCCs (Kasperlik-Zaluska et al. 2006). Few multi-organ endocrine neoplastic syndromes such as Multiple Endocrine Neoplasia (MEN) 2A and 2B, Von Hippel-Lindau (VHL) disease and neurofibromatosis type 1 can have PCCs/PGLs as disease manifestations (Pappachan et al. 2014; Desai et al. 2009). Hypertensive crisis during emergency surgery, general anaesthesia or contrast radiography, unexplained heart failure, drug-induced hypertensive crisis (with beta-blockers or monoamine oxidase inhibitors), and new-onset diabetes in an young lean hypertensive are some of the atypical clinical presentations of the disease (Pappachan et al. 2014).

Diagnostic Approach

Biochemical As in any other endocrine disease biochemical confirmation of the diagnosis is the first-line approach to the diagnosis of PCCs/PGLs. Plasma free metanephrines or urinary fractionated metanephrines is the screening investigation of choice for suspected cases with very high sensitivity and good specificity (Pappachan et al. 2014; Lenders et al. 2014). Intake of multiple medications and other chemicals before testing can interfere with the results reducing the positive predictive value of this screening assay. A detailed list of these medications can be found in the relevant literature (Pappachan et al. 2014; Lenders et al. 2014). Therefore, raised levels $\leq$ 3–4 times the laboratory reference range should be interpreted with caution to avoid un-necessary work up because of a false positive test. A clonidine suppression test may be useful in such situations (Lenders et al. 2014; Eisenhofer et al. 2003).

Anatomical Imaging Imaging studies for localisation should only be undertaken after the biochemical diagnosis is proven. CT scan and Magnetic Resonance Imaging (MRI) have excellent sensitivity and reasonable specificity for anatomical localisation of these tumours. Non-ionic contrast is preferred for CT scan because of the risk of hypertensive crisis (Lenders et al. 2014). MRI is preferred over CT in patients in whom where radiation needs to be avoided and in patients suspected to have metastatic disease (Pappachan et al. 2014; Lenders et al. 2014).

Functional Imaging Once the anatomical diagnosis is established with an initial imaging

modality, functional imaging is usually recommended to prove the diagnosis, and to exclude the possibility of metastasis and multi-site disease in cases of PGLs. ^{123}I-metaiodobenzylguanidine (MIBG) scitigraphy is the usual functional imaging modality utilized in most centers. The sensitivity and specificity of ^{123}I-MIBG scintigraphy is around 85 % in PCCs. A variety of different radio-pharmaceutical agents can be used for functional imaging in cases with a negative ^{123}I-MIBG scintigraphy (Pappachan et al. 2014; Lenders et al. 2014).

Genetic Testing The recommendations for genetic testing and the testing algorithm can be found in the 2014 Endocrine society guidelines (Lenders et al. 2014).

An algorithm for diagnostic work up of clinically suspected PCCs/PGLs is shown in Fig. 2.

Management Surgery is the preferred definitive management option for all cases of PCCs/PGLs unless contraindicated. Complete resection of the tumor often results in cure of the disease although improvement in hypertension depends on other factors too.

Peri-Operative Management

Prompt control of hypertension and appropriate preoperative preparation is a must as manipulation of the tumour during surgery results in hypertensive crisis because of the massive release of catecholamines to circulation. Adequate control of hypertension with non-selective α-adrenergic blockers such as phenoxybenzamine (10 mg BD to a maximum of 1 mg/kg/day) or α-1 selective agent doxazosin (2–32 mg/day) 10–14 days prior to the surgery along with liberal intake of fluids and salt to replenish volume depletion is recommended in

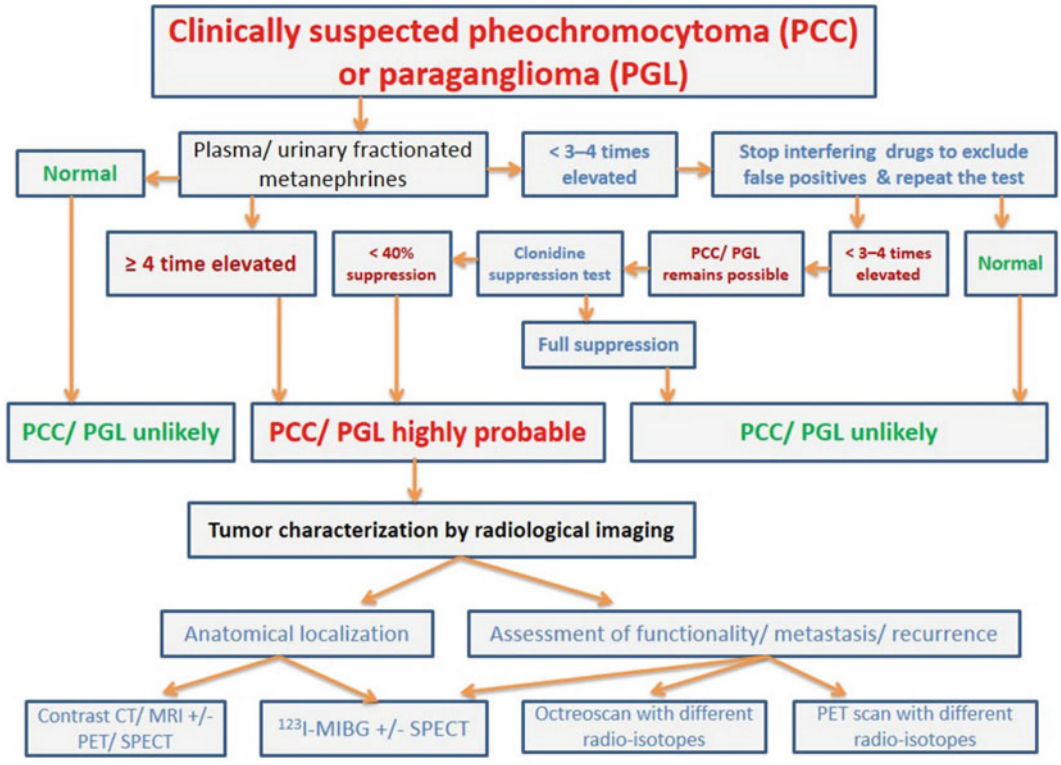

Fig. 2 Diagnostic evaluation of pheochromocytomas (PCCs) and paragangliomas (PGLs) (*CT* Computed tomography, *MRI* Magnetic resonance imaging, *PET* Positron emission tomography, *SPECT* Single photon emission computed tomography, ^{123}*I-MIBG* ^{123}Iodine-Meta-iodo-benzyl-guanidine. Reproduced with permission from Pappachan et al. (2014))

all cases (Pappachan et al. 2014; Lenders et al. 2014). Addition of a β-adrenergic blocker such as propranolol or atenolol to counteract the reflex tachycardia and postural hypotension associated with α-blockers may be necessary after few days of starting α-blockers. Other antihypertensive medications such as calcium channel antagonists and metyrosine may be necessary for optimal control of BP in some cases (Pappachan et al. 2014; Tsirlin et al. 2014; Lenders et al. 2014). The target BP control should be < 130/80 mm Hg while seated and > 90 mm systolic while standing and a heart rate 70–80 per minute (Pappachan et al. 2014; Tsirlin et al. 2014; Lenders et al. 2014). Appropriate modifications in these targets may be made in the presence of cardiovascular disease.

Operative Management Surgeon and anaesthetist with sufficient experience with the management of these rare tumors should perform the surgery to optimise safe outcomes. Laparoscopic adrenalectomy is the preferred surgery in most cases of PCCs. Large tumors, PGLs and suspected metastatic disease are indications for an open surgery (Pappachan et al. 2014; Tsirlin et al. 2014; Lenders et al. 2014). Intra-operative BP changes should be closely monitored with administration of intravenous α-adrenergic blockers (phentolamine or phenoxybenzamine) for hypertensive episodes during surgery, and intravenous crystalloids and vasopressors to manage the postoperative hypotension in an intensive care unit may be necessary to manage cases (Pappachan et al. 2014; Tsirlin et al. 2014).

Postoperative Care Withdrawal of the antihypertensive medications and hypoglycemic agents (if secondary diabetes was present pre-operatively) may be possible in some cases. Testing plasma (or urinary) metanephrines 10 days after the surgery to ensure complete removal of the tumor is recommended in all cases (Pappachan et al. 2014; Tsirlin et al. 2014; Lenders et al. 2014). Regular endocrine follow up of the patients with appropriate long-term care plan is also mandatory.

Follow Up The follow up care of patients with PCCs and PGLs is detailed in the 2014 guidelines of the Endocrine Society (Lenders et al. 2014).

An algorithm for management and follow up of PCCs/PGLs is shown in Fig. 3.

6 Glucocorticoid Excess (Cushing's Syndrome)

Glucocorticoids are hormones from the zona fasciculata of the adrenal cortex. Although physiological levels are critically important for homeostasis in normal subjects, excess production of glucocorticoids in the body (endogenous hypercortisolism) or prolonged administration of the hormone in high doses (iatrogenic hypercortisolism) result in a pathologic state known as Cushing's syndrome (CS) that is associated with protean manifestations including secondary hypertension. The disease is associated with excess morbidity, mortality and poor quality of life, and an early diagnosis and appropriate management may mitigate this natural history (Nieman 2015). The clinical picture of CS cases varies depending on the extent and duration of cortisol excess.

Pathophysiology

A majority of cases of CS results from an ACTH producing pituitary adenoma that is otherwise known as Cushing's disease. Ectopic production of ACTH accounts for a significant proportion of cases other than pituitary Cushing's, followed by cortisol-secreting adrenal adenomas and carcinomas, and adrenal nodular hyperplasia. Exogenous steroid administration for therapeutic purposes results in iatrogenic CS in many patients. Carney complex, a rare genetic disorder (autosomal dominant), characterized by pigmented skin and mucosal lesions, cardiac and cutaneous myxomas, and multiple endocrine and non-endocrine neoplasms is an uncommon cause of CS (Correa et al. 2015). Another rare cause for CS is ectopic CRH (corticotropin releasing hormone) producing tumors. Subclinical CS, results from alterations in the hypothalamus–pituitary–adrenal (HPA) axis without overt signs or symptoms of hypercortisolism (Di Dalmazi et al. 2015).

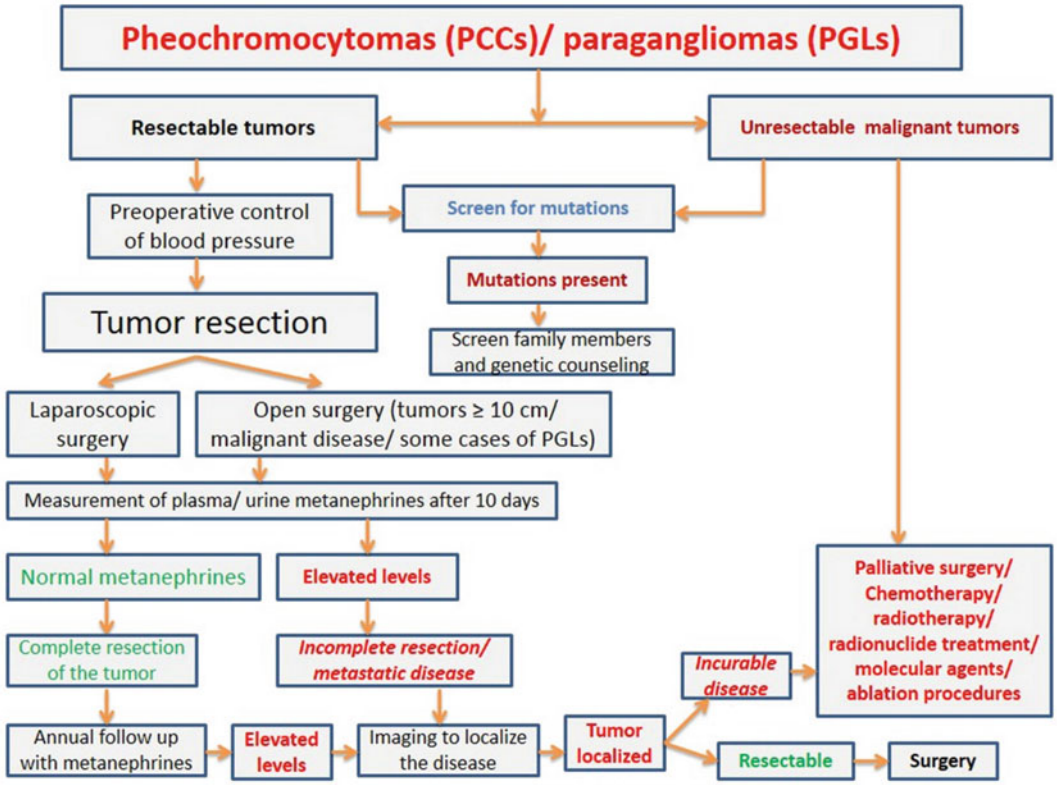

Fig. 3 Management and follow up care of pheochromocytomas (PCCs) and paragangliomas (PGLs) (Reproduced with permission from Pappachan et al. (2014))

Hypertension in CS may be multi-factorial, and the exact mechanisms still remain elusive. Several putative mechanisms have been identified including imbalance between vasodilatory and vasoconstrictor chemicals such as prostacyclin, nitric oxide and endothelins, the mineralocorticoid receptor activation (Di Dalmazi et al. 2015; Anagnostis et al. 2009; Mihailidou et al. 2009; De Leo et al. 2010; Rizzoni et al. 2009), endothelial abnormalities (Di Dalmazi et al. 2015; Anagnostis et al. 2009), and development of metabolic syndrome (Di Dalmazi et al. 2015; Anagnostis et al. 2009; Ferraù and Korbonits 2015).

Clinical Features

A wide variety of clinical manifestation may be seen in a classical case of overt CS (Nieman 2015). These include facial plethora, fragility of skin, acne, hirsutism, thinning of scalp hair, weight gain with truncal obesity, buffalo hump and supraclavicular fatty pad (due to ectopic fat distribution), labile mood and sometimes frank psychosis, menstrual irregularities, proximal myopathy, growth failure in children, sexual dysfunction (and even impotence), hypertension, hypokalaemia, glucose intolerance or frank diabetes, osteoporosis, metabolic syndrome, and susceptibility to infections due to suppressed immunity. However, these classical manifestations are less frequently observed these days because of wide availability of investigations and awareness of the disease among physicians. In up to 15 % of adults with CS, the clinical manifestations may occur only periodically, a condition known as cyclical Cushing's syndrome (Alexandraki et al. 2009).

Diagnostic Approach

Although the American Endocrine Society Guidelines on diagnostic evaluation of CS is slightly old (Nieman et al. 2008), most of the recommendations are still valid for work up of suspected cases. An exclusive meeting to discuss about CS, held in Germany in October 2014 with wide participation from global experts, compiled further evidence on the diagnostic and management algorithms of the disease (Reincke 2015). A detailed discussion of the diagnostic approach to CS can be found in these published literature and only a brief account is given here.

A thorough history of extraneous steroid administration should be obtained in all cases of clinically suspected CS before biochemical testing. The Endocrine society recommends testing for CS in patients with multiple clinical features described above, children with growth retardation with abnormal weight gain, illnesses uncommon in younger age-groups such as hypertension and osteoporosis, and adrenal adenomas (Nieman et al. 2008).

In suspected cases of CS, one of the following screening investigations should be performed initially: 24-hour urinary free cortisol (at least 2 samples), late night salivary cortisol, 1-mg overnight dexamethasone suppression test (DST) or low-dose DST (0.5 mg QDS for 48 h) (Nieman et al. 2008). Further evaluation by an endocrinologist is recommended in cases with at least one positive test and in those with negative screening tests and clinically suspected cyclical CS. Random plasma cortisol measurement has no value for screening cases of CS because of the marked variability of levels depending of many factors.

Confirmation of CS in suspected cases needs detailed endocrine work up. Measurement of corticotrophin (ACTH) levels is the next step in diagnosis. Suppressed level of ACTH indicate an adrenal/iatrogenic source of hypercortisolism. If adrenal source is suspected a contrast CT scan of the adrenal glands should be done. If ACTH levels are high or high normal, an MRI of pituitary should be done. A pituitary mass $\geq$ 1 cm may be an indication of Cushing's disease and pituitary surgery although controversy still remains among endocrinologists on size criteria (Florez et al. 2013). A high-dose DST (using 2 mg QDS for 48 h) and/or CRH stimulation tests is recommended by some centers if the pituitary mass is smaller or absent, in presence of raised ACTH levels. A suppressible cortisol with high-dose DST or 20 % rise in cortisol following CRH administration indicates pituitary-driven corticotrophin excess although overlap with ectopic source is well recognised. Bilateral inferior petrosal sinus sampling (BIPSS) with baseline and CRH-stimulated ACTH measurements is the next step. If BIPSS is negative, imaging of thorax and/or abdomen and pelvis should be performed to identify an ectopic source of ACTH. Finally, an octreotide scan may be necessary if all other confirmatory tests are negative. A useful algorithm for diagnostic work up of CS can be found in the full-test article (freely available) by Florez et al. (2013).

Management

Management of CS can be complex in many cases, and the mortality related to the disease is reported to be higher than in normal age-matched controls even in treated cases (Clayton et al. 2011; Graversen et al. 2012). Complete cure of the disease may not be always possible, and management of disease manifestations shall be the only options in such cases. Whenever feasible, surgical removal of the cause of excess cortisol/ACTH is the most appropriate and potentially curable management option.

Medical Therapy Even in curable cases, medical management should bridge the definitive surgery for adequate preparation of the patient. First-line agent widely used is metyrapone, a 11-β-hydroxylase enzyme inhibitor (dose range 1–4 g/day in divided doses). The drug has been found to be very effective for short- and long-term control of endogenous steroid excess in a recent multicenter study (Daniel et al. 2015). However, the drug can increase the adrenal synthesis of steroids with mineralocorticoid activity

that worsens hypertension (Ferraù and Korbonits 2015). Other cortisol-lowering medications such as ketoconazole (Nieman 2002), mitotane (Donadille et al. 2010) and mifepristone (Fleseriu et al. 2012) also have beneficial effects on hypertension in CS, although careful monitoring for side effects of these agents is necessary. Recent guidelines from the Endocrine Society and recommendation from the European Medicines Agency suggest ketoconazole as highly effective option for medical management of CS when used judiciously (European Medicines Agency 2016; Nieman et al. 2015). Combination therapy with ketoconazole and metyrapone may be necessary to obtain rapid control hypercortisolism in some cases (Nieman et al. 2015). Pasireotide alone (Colao et al. 2012), or in combination with cabergoline and ketoconazole (Feelders et al. 2010) also have been reported to benefit treatment of hypertension in CS. Recently, retinoic acid (Pecori Giraldi et al. 2012) and LCI699 have been shown to be effective in treatment of CS and disease-related hypertension (Bertagna et al. 2014; Daniel and Newell-Price 2015). Along with medical measures to manage hypercortisolism, conventional antihypertensive treatment also needs to be administered for control of BP in patients with CS.

Surgery Transphenoidal hypophysectomy is the preferred surgical treatment in Cushing's disease although cure is not guaranteed in all cases owing to the difficulty in removal of the entire tumour tissue in some cases, especially small adenomas. Pituitary radiotherapy may be necessary in selected cases with residual tumour although associated with higher long-term complication rates including pan-hypopituitarism. Functional imaging of the pituitary with (11)C-methionine positron emission tomography-computed tomography (PET-CT) scan is recently reported to be an excellent tool to localise residual disease after previous hypophysectomy for targeted therapy (Koulouri et al. 2015).

Removal of the source of ectopic ACTH-driven CS may be easy if precise tumour localisation is possible pre-surgically.

Hypophysectomy with or without pituitary radiotherapy is usually associated with multiple pituitary hormone insufficiencies that necessitates lifelong hormone replacement with endocrine follow up. Sometimes bilateral adrenalectomy may be necessary for patients with intractable CS where source of ACTH excess is irremovable (Reincke et al. 2015). This surgery is reported to be relatively safe and highly effective in such cases. Patients need lifelong steroid and mineralocorticoid replacement and Nelson's syndrome is a possible consequence of this surgery in CS due to the growth of the pituitary adenoma in absence of feedback inhibition from corticosteroids.

7 Acromegaly

Acromegaly results from prolonged growth hormone (GH) excess in adults. GH exerts its hormonal effect in the body through the protein molecule Insulin-like Growth Factor-1 (IGF-1) secreted from liver. The classical cases of acromegaly with all the phenotypic features are less often encountered currently in clinical practice owing to better investigation facilities and heightened awareness of the disease among physicians that result in early diagnosis of the disease. The estimated prevalence of the disease is 30–60 cases/one million population and arterial hypertension is encountered in 40 % of the cases (Capatina and Wass 2015).

Pathophysiology

In over 95 % of cases, acromegaly results from a GH-secreting somatotroph adenoma of pituitary causing GH and IGF-1 overproduction (Melmed 2009; Katznelson et al. 2014). Majority of these are macroadenomas (size $>$ 1 cm). Less than 5 % of cases results from a hypothalamic tumour or a neuroendocrine tumour secreting Growth Hormone Releasing Hormone (GHRH) or rarely GH overproduction from a hemopoeitic or abdominal tumor (Katznelson et al. 2014). GH-producing tumours may be a consequence of the genetic MEN-1 syndrome.

Overstimulation from the excess GH in circulation results in raised plasma levels of IGF-1 produced from liver that causes overgrowth of somatic tissues culminating in the clinical manifestations of acromegaly. Disfigurement of the facial skeleton and enlargement of limbs result from prolonged hyper-stimulation of IGF-1. The clinical manifestations of the disease are related to overgrowth of tissues and the metabolic abnormalities related to excess circulating IGF-1 levels.

Clinical Features

The disease affects most body organs and the common manifestations are headache, coarse facial features (frontal bossing and prognathism), enlargement of hands and feet, hypertension and diabetes, osteoarthritis, entrapment neuropathies, sleep apnoea, visual field defects and heart failure. A detailed account of the disease and its clinical features can be found in the recent article (available free in the web) by Capatina et al. (2015).

Diagnostic Approach

All patients with clinically suspected acromegaly and typical features should undergo testing for IGF-1 levels. Those with some of the features without a definite clinical picture may also need IGF-1 testing when some of disease-associated features such as sleep apnoea, type 2 diabetes, hypertension, carpel tunnel syndrome, debilitating arthritis or hyperhidrosis are present (Katznelson et al. 2014). IGF-1 levels also should be measured in patients with a pituitary mass to exclude the disease. Biochemical confirmation of acromegaly in patients with elevated or equivocal IGF-1 levels is by a glucose tolerance test to show lack of suppression of GH levels during hyperglycemia (Capatina and Wass 2015; Katznelson et al. 2014).

In biochemically confirmed cases, disease localisation should be done by an appropriate imaging study. An MRI of the pituitary detects a macroadenoma in about 77 % cases (Katznelson et al. 2014; Mestron et al. 2004), and a hyper-intense T2-weighted MRI signal may have prognostic significance (enhanced response to somatostatin receptor ligand [SRL] therapy) (Katznelson et al. 2014; Puig-Domingo et al. 2010). Visual field testing is recommended in all cases with a pituitary macroadenoma in the MRI. If pituitary imaging is negative, GHRH levels should be measured to exclude rare location of the disease in hypothalamus or other tissues with appropriate imaging when necessary (Capatina and Wass 2015).

Management

Surgery All resectable tumors in the pituitary should be removed through a transphenoidal hypophysectomy if possible. Some large tumors may need a trans-cranial or combined approach. Sometimes surgical de-bulking improves the medical treatment outcome later if complete removal of the tumor is impossible (Katznelson et al. 2014; Katznelson 2010). Repeated surgery may be necessary if initial procedure did not clear the entire tumor. Postoperative measurement of GH and IGF-1 levels give evidence for clearance of tumor during surgery and pituitary imaging is necessary for anatomical assessment. These are usually done after 12 weeks of surgery (Katznelson et al. 2014).

Medical Treatment Medical management becomes necessary when tumors are inoperable or when surgery is incomplete with residual disease. SRLs and pegvisomant are the two classes of drugs with good activity against acromegaly. 2 forms of SRLs are commercially available widely (Octreotide LAR [long acting release] and lanreotide depot/autogel). Pasereotide is a novel SRL with enhanced activity and confers better tumoral response to treatment (Capatina and Wass 2015; Katznelson et al. 2014; Colao et al. 2014). Pegvisomant possess better treatment response than SRLs in patients with acromegaly (Katznelson et al. 2014; van der Lely et al. 2012). Monitoring of response to treatment and dose adjustments are done with serial measurements of IGF-1 and pituitary imaging.

Mild disease may respond to dopamine agonists such as cabergoline. Combinations of different drug classes in different multi-drug regimes may be necessary in some cases for enhanced response to treatment (Capatina and Wass 2015; Katznelson et al. 2014). Pituitary radiotherapy may also be necessary in cases with residual disease when medical therapy fails to control the disease.

Management of multi-system manifestations of the disease such as diabetes, hypertension, entrapment neuropathy and heart disease should be as per the individual needs of the patient. In general, acromegaly cases are managed in a multi-disciplinary team environment involving endocrinologists, surgeons, biochemists and anaesthesiologists with significant expertise in the management of this uncommon disease.

8 Thyroid Diseases

Thyroid disorders are the second most common causes of endocrine disease after diabetes mellitus. Although not associated with severe hypertension, both hypothyroidism and hyperthyroidism can cause high BP in some patients.

8.1 Hypothyroidism

Hypothyroidism is a common endocrine disease with higher prevalence towards older age-groups. Subclinical hypothyroidism (without overt symptoms and signs) affects about 3-8 % of adult population that reaches around 10 % by the sixth decade of life (Hollowell et al. 2002; Fatourechi 2009). Overt hypothyroidism presents with multiple clinical features such as lethargy, constipation, cold intolerance, menstrual abnormalities, weight gain, dry skin, hair loss, hoarseness of voice, psychomotor retardation, neuropsychiatric abnormalities, bradycardia and in severe cases, myxedema and coma.

Bradycardia, mild hypertension, narrow pulse pressure, and muffling of heart sounds are the most common signs of overt hypothyroidism (Klein and Ojamaa 2001). Positive correlation between serum thyrotropin levels and hypertension was observed in children and adolescents, suggesting a linear relationship between even subclinical hypothyroidism and BP, in two large cohort studies among two populations with entirely different genetic backgrounds (Chen et al. 2012; Ittermann et al. 2012). High serum thyrotropin levels were positively associated with systolic and diastolic blood pressure, in children and adolescents with Odds ratios 1.12 and 1.19 respectively ($p < 0.05$ in both) (Ittermann et al. 2012). Appropriate control of hypothyroid state with thyroid hormone replacement results in normalisation of blood pressure as many of the other abnormalities related to the disease.

8.2 Hyperthyroidism

Hyperthyroidism results from excessive circulating levels of thyroid hormones. Primary hyperthyroidism from diseases of the thyroid gland is usually autoimmune. Subclinical hyperthyroidism, a state of suppressed thyrotropin levels and normal thyroid hormones, is seen in up to 1 % of men and 1.5 % of women older than 60 years (Ittermann et al. 2012; Helfand 2004). The clinical features of hyperthyroidism are mostly opposite to hypothyroidism, familiar to most physicians, and therefore, not described here.

Hyperthyroidism increases cardiac output by 50–300 % because of a decrease in systemic vascular resistance, an increase in heart rate, increase in left ventricular output, and an increase in the blood volume (Klein and Ojamaa 2001). Therefore, systolic hypertension with a widened pulse pressure (opposite to the hypothyroid state) is the usual clinical manifestation in hyperthyroidism. Prompt resolution of hypertension is usually observed in patients with hyperthyroidism after full control of the disease by medical or surgical intervention.

9 Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) results from increase in secretion of parathyroid hormone (PTH) from the parathyroid glands. The estimated incidence of PHPT in the United States from 1993 to 2001 was approximately 22 cases per 100,000 person years (Wermers et al. 2006; Marcocci and Cetani 2011). Prevalence of PHPT can be as high as 2.1 % on older individuals (Lundgren et al. 1997). Many cases are asymptomatic, and the diagnosis is often made while investigating patients for the cause of mild hypercalcemia. Sometimes patients may present with severe hypercalcemia, renal stones, osteoporosis and fractures, acute kidney injury, and chronic renal impairment.

Frequent association between PHPT and hypertension is well documented even among patients with mild PHPT (Silverberg et al. 2009). Mean 24-h BP (both systolic and diastolic) obtained by ambulatory monitoring was significantly higher, with a higher prevalence of hypertension in 47 % of patients with PHPT compared to controls (Letizia et al. 2005). Plasma ionised calcium levels was found to be an independent risk factor for elevated BP in multiple linear regression model in this study. The probable mechanism of hypertension in PHPT is increased arterial stiffness in these patients. A recent large community-based cohort study indicated that plasma calcium levels were independently associated with higher arterial stiffness, and the PTH levels with arterial blood pressures (Hagström et al. 2015).

Generally, mild cases of PHPT are not treated by parathyroid surgery, and the follow up is with regular monitoring of calcium, renal function and bone mineral density assessments in the endocrine outpatient clinics. Hypertension is managed by conventional antihypertensive drugs as in a normal case. Thiazide diuretics should be avoided as antihypertensives because of the risk of worsening hypercalcemia. There is conflicting data on the improvement of hypertension in patients undergoing parathyroidectomy for PHPT with some studies showing benefit (Nainby-Luxmoore et al. 1982; Ringe 1984; Broulik et al. 2011), while others without a positive effect (Rapado 1986; Lind et al. 1991). Although improvement of the substantial cardiac and vascular dysfunction related to symptomatic PHPT was observed in patients after parathyroidectomy (Agarwal et al. 2013), PHPT-related hypertension is not an indication for surgery currently.

10 Iatrogenic Hormone Manipulation

Therapeutic administration of hormones for different medical conditions can result in development of/or worsening of hypertension. Glucocorticoid administration is the most common cause for drug-induced endocrine hypertension. Prevalence of Steroid-induced hypertension increases with age, and new-onset hypertension was observed in 22 % of cases receiving long-term steroids for giant-cell arteritis (Proven et al. 2003). Studies on the effect of hormone replacement on hypertension in post-menopausal women showed conflicting results with positive (Preston 2009), and negative effects (Akkad et al. 1997). Although testosterone can theoretically increase BP by the effects of vasoconstriction and stimulation of renin-angiotensin-aldosterone system (Kienitz and Quinkler 2008), testosterone replacement resulted in improvement of the parameters of metabolic syndrome including hypertension in hypogonadal men (Janjgava et al. 2014).

A classification of different endocrine disorders causing hypertension, their common clinical presentations, important diagnostic features and treatment are summarized in Table 1.

11 Conclusions

Endocrine hypertension is a cause of secondary hypertension in a significant proportion of cases. Some clinical characteristics of the patients may

Table 1 The causes of endocrine hypertension, their common clinical characteristics, diagnostic features & treatment

Clinical condition				Common clinical characteristics	Diagnostic features	Treatment
Primary mineralocorticoid Excess	***Hypermineralocorticoidism***	**Primary aldosteronism**	***Aldosterone producing adenoma (APA)***	Resistant HTN & adrenal adenoma	Raised ARR, CT – adrenal adenoma, AVS – lateralisation to side of adenoma	Adenoma removal/MR antagonist
			Idiopathic hyperaldosteronism	Resistant HTN	Raised ARR, CT adrenal – negative	MR antagonist
			Type 1 familial hyperaldosteronism (FH-I)	Resistant HTN and strong family history	Raised ARR; HTN & aldosterone suppressed by dexamethasone	Glucocorticoid therapy
		Congenital adrenal hyperplasia	***11-β-hydroxylase deficiency***	HTN, virilisation and precocious puberty	Elevated DOC & 11-deoxycortisol. Abnormal genes	Glucocorticoids; (MR antagonists in some cases)
			17-α-hydroxylase deficiency	Hypokalemia, HTN & sexual infantilism	High ACTH, DOC & gonadotropins, low androgens, estrogens. Abnormal genes	Glucocorticoids & sex steroids when necessary
	Increased minrealocorticoid action	**Liddle syndrome (pseudo-aldosteronism)**		HTN, hypokalemia & alkalosis with family history	Low aldosterone & rennin, ENaC gene mutation	Low sodium diet + amiloride or triamterine
		Syndrome of apparent mineralocorticoid excess (AME)		Hypokalemia, HTN, & alkalosis. Severe disease: growth failure and short stature in children	Low aldosterone & renin, high ratio of urine cortisol/cortisone metabolites & HSD11B2 gene mutation	MR antagonists +/− thiazide diuretics & small doses of dexamethasone
		Pseudohypoaldosteronism type 2 (Gordon syndrome)		HTN, hyperkalemic-hyperchloremic metabolic acidosis	low renin, normal or elevated aldosterone level, abnormal gene mutations	Dietary sodium restriction and thiazide diuretics
		Geller syndrome		Early onset HTN & worsening of HTN during pregnancy	Low plasma aldosterone & renin & activating mutation of MR	Sodium restriction & amiloride for HTN

Pheochromocytomas and paragangliomas (PCC & PGL)		Episodic symptoms with HTN. Adrenal incidentaloma	High plasma and urinary metanephrines. PCC or PGL on imaging	Tumor removal with surgical precautions. Long-term follow up
Glucocorticoid excess (Cushing's syndrome)		HTN with cushingoid appearance, diabetes, metabolic syndrome, infection susceptibility & osteoporosis	High plasma and urinary cortisol, ACTH – high in central & ectopic; low in adrenal Cushing's. Imaging evidence of source of high ACTH or adrenal disease.	Metyrapone, antihypertensives, surgery to remove ACTH source or adrenalectomy
Acromegaly		Coarse body features with facial & limb enlargement, HTN, diabetes, sleep apnoea, visual field defects & arthritis	High levels of insulin-like growth factor 1 & growth hormone (GH), lack of GH suppression on glucose tolerance test & pituitary adenoma on imaging	Pituitary adenoma removal by surgery if possible. GH suppression by SRL therapy & antihypertensives
Thyroid diseases	***Hypothyroidism***	Diastolic HTN, weight gain & coarse features	High levels of thyrotrophin with low/low-normal level of thyroid hormones	Thyroid hormone replacement
	Hyperthyroidism	Systolic HTN with weight loss	Low levels of thyrotrophin with high/high-normal level of thyroid hormones	Antithyroid drugs, thyroidectomy/radio-iodine therapy
Primary hyperparathyroidism		HTN, asymptomatic disease in many, fractures & osteoporosis, acute/chronic renal failure	Hypercalcemia with raised parathyroid hormone level and parathyroid adenoma or hyperplasia	Parathyroidectomy in selected cases. Close monitoring & periodic evaluation in mild cases
Iatrogenic hormone manipulation		HTN with history of hormone treatment	History and blood pressure elevation	Antihypertensives and withdrawal of hormone if feasible

HTN hypertension, *ARR* aldosterone to renin ratio, *MR* mineralocorticoid receptor, *ENaC* epithelial sodium channel, *CT* computed tomography, *ACTH* adrenocorticotrophin

help clinician to suspect an endocrine cause for hypertension. Primary aldosteronism is the most common cause for endocrine hypertension. The Endocrine society guidelines on individual diseases that cause endocrine hypertension may help clinician to appropriately evaluate and manage patients.

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