

SECONDARY HYPERTENSION

Introduction

Specific causes of hypertension can be diagnosed in less than 10% of patients with established hypertension (Tables 1-5 and Figure 1). An additional very common cause is sleep apnoea. Early onset of hypertension (i.e. <30 years), resistant hypertension or severe hypertension, non-dipping or reverse dipping during 24 h ambulatory BP monitoring, and presence of target organ damage suggest secondary hypertension.¹ Up to 35% of elderly patients with secondary hypertension do not respond to specific therapy.

Obstructive sleep apnoea

Obstructive sleep apnoea is one of the most common causes of secondary hypertension (5-15%), mainly associated with hypertension in patients <60-year old.^{2,3} Most patients with complain of exaggerated daytime sleepiness, snoring, morning headache, lack of concentration, and irritability. Typical clinical findings are obesity, large neck, and macroglossia. Both nocturnal (non-dipping) and daytime blood pressure are increased (Figure 2). Patients often display significant tachycardia and/or bradycardia during nighttime probably due to hypoxemia-induced autonomic activity alterations. Continuous positive airways pressure (CPAP), but not nocturnal oxygen supplement alone, and weight loss are recommended for sleep apnoea, and may result in decreases of blood pressure, especially nocturnal. There is a poor compliance with CPAP, however, and this kind of therapy does not affect cardiovascular mortality.^{4,5} Sleep apnoea stimulates atrial natriuretic peptide release with resultant nocturnal diuresis and sympathetic nerve activity; thus β blockers are more efficacious than thiazides, but ACE inhibitors and ARB have been equally effective in some studies.⁶

Renal Parenchymal Disease

Renal parenchymal disease (2-8%) is due to diabetic nephropathy, hypertensive nephrosclerosis that by itself further increases blood pressure, polycystic kidney disease, and chronic glomerulonephritis. *Kidney ultrasound* (for kidney size, cortical thickness, urinary tract obstruction, and cysts or masses), assessment of *serum creatinine*, *electrolytes*, and *urinalysis* for red and white blood cells and proteinuria are essential initial tests in all patients with established hypertension. In hemodialysis patients (lack of renin activity) hypertension is labile and sensitive to changes in fluid volumes. Acute renal disease such as acute

glomerulonephritis or urinary tract obstruction may also result in hypertension. Therapy is discussed in the previous Chapter.

Renovascular Hypertension

This is also a relatively common cause of secondary hypertension (1-8%) (Table 6 and Figure 2)

However, renal artery stenosis is difficult to prove to be the cause of hypertension.^{7, 8} Clinical clues for such an association are:

- Resistant hypertension
- Sudden onset of hypertension before 50 years of age
- Negative family history for hypertension
- Generalized atherosclerosis
- Hypokalemia
- Deterioration of renal function with ACEI/ARB

A decrease in renal perfusion pressure activates the renin–angiotensin system, which leads to the release of renin and the production of angiotensin II, has direct effects on sodium excretion, sympathetic nerve activity, intrarenal prostaglandin concentrations, and nitric oxide production, and causes renovascular hypertension. When hypertension is sustained, plasma renin activity decreases, partially explaining the limitations of renin measurements for identifying patients with renovascular hypertension.⁸

Aetiology

Two forms of renal artery stenosis are described in adults:

Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm, or dissection.⁹ It is primarily seen in women, and most commonly affects the renal (usually distal two thirds), carotid, and vertebral arteries but may occur in virtually every artery of the body. It is the second most frequent cause of renovascular hypertension (10-15% of cases). Renal Doppler detects dysplasia but instead of one area of stenosis as usually happens in atherosclerosis, there are multiple areas of stenosis making the low characteristics different. CT scanning is also useful, but the gold standard remains catheter-based angiography.⁹ A cerebrovascular event including transient ischemic attack, stroke, and/or amaurosis fugax occurs in 25% of patients.¹⁰ The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of the condition.

Atherosclerotic disease (85-90%) involving the proximal one third of the main renal artery is usually seen in old men. ACEI and ARB are effective in these patients, but the loss of renal mass and reduction in transcapillary filtration pressure can produce acute or chronic renal

insufficiency, especially if renal-artery stenosis affects both kidneys or the sole functional kidney. Medical therapy consists of diuretics, CCBs, ACEI/ARB (in the absence of bilateral stenosis) and statins.

Rare causes are aortic dissection with renal artery involvement, acute renal artery occlusion (thrombosis, embolism or trauma), Takayasu or giant cell arteritis, congenital mid-aortic syndrome, and antiphospholipid antibodies syndrome.

Diagnosis

Kidney ultrasonography may show a difference of more than 1.5 cm in length between the two kidneys in 60–70% of the patients with renovascular hypertension and is diagnostic for renal artery stenosis (Table 9). **Doppler ultrasonography** is capable of detecting stenosis, particularly when localized proximally, but gadolinium enhanced **MRI** is considered the diagnostic procedure of choice, but is contraindicated in the presence of $\text{GFR} < 30 \text{ ml/min}$. **CT angiography** may also be used with a $\text{GFR} \geq 30 \text{ ml/min}$.¹¹ Significant renal artery stenosis is defined as $\geq 50\%$ diameter stenosis, associated with peak translesional gradient $\geq 20 \text{ mm Hg}$, or a mean gradient $\geq 10 \text{ mmHg}$.⁷ However, both arteriography and Doppler measurements overestimate renal artery stenosis as defined by detection of a distal renal to aortic pressure ratio of < 0.9 .¹²

Therapy

Angioplasty with stenting or surgical revascularization are not recommended any more for atherosclerotic renovascular disease (Table 7 and Figure 3).¹³⁻¹⁵ Medical therapy for control of hypertension and high-intensity statins are indicated. Angioplasty or surgical revascularization has also yielded moderate benefits in patients with fibromuscular dysplasia renal artery stenosis,¹⁶ although angioplasty without stenting appears to be the best therapeutic option.¹⁵ The condition also responds to ACEI and ARB therapy. Significant increase of creatinine with a small dose of ACEI/ARB suggests bilateral renal artery stenosis. Anatomically relevant renal artery stenosis $> 70\%$ should be verified by functional measurements as systolic pressure gradient $\geq 21 \text{ mmHg}$ or Pd/Pa pressure ratio < 0.9 .¹² The best evidence supporting intervention may be for bilateral stenosis with ‘flash’ pulmonary oedema unrelated to acute coronary syndrome (Pickering syndrome).^{17, 18} FFR (< 0.80) is a credible indication for stenting.¹⁹

Primary Aldosteronism

Primary aldosteronism is defined as inappropriately elevated aldosterone production in the setting of low plasma renin.²⁰ In renin-independent aldosteronism there is production of aldosterone from one or both adrenal glands, independent of regulation by renin and angiotensin II, which results in inappropriate activation of the mineralocorticoid receptor

(MR) and its downstream consequences. It can be detected in 20% of patients with hypertension, $\geq 25\%$ of those with resistant hypertension or hypertension with diabetes, and $\geq 28\%$ of those with hypertension and hypokalemia.^{21, 22} Its pathology spans a wide spectrum, that includes bilateral adenomas, unilateral hyperplasia, micronodules, and microscopic aldosterone-producing cell clusters, in various combinations. Three types of familial hyperaldosteronism have been described, and in many cases, somatic mutations in aldosterone production are involved.²⁰ Aging seems to be associated with a subclinical form of aldosterone excess.²³ Subclinical primary aldosteronism (a renin concentration ≤ 4.0 ng/L and an aldosterone-to-renin ratio ≥ 70 pmol/L per ng/L) is negatively associated with cardiovascular events even in normotensive people.^{24, 25}

Diagnosis

Patients with drug-resistant hypertension and lone AF should be tested for primary aldosteronism.²⁶ The condition should also be suspected in resistant hypertension and in unprovoked hypokalaemia, but only a small number of patients will have hypokalaemia at an early stage in their disease (Table 11). Increased **urinary excretion of potassium** (>30 mmol/day in the presence of hypokalemia and in the absence of extra potassium intake) points to aldosteronism. Initially, patients suspected for primary aldosteronism can be screened without interrupting medications.²⁰ **Plasma renin activity** (PRA) < 1 ng/(ml⁻¹ × h⁻¹), or direct renin concentration < 10 pg/ml, together with an **aldosterone** >20 ng/dl indicate primary aldosteronism. Aldosterone values of 10-20 ng/dL are borderline. Aldosterone can be high or the renin low in elderly people or black patients. If cases of high suspicion, such as when renin remains suppressed despite mineralocorticoid receptor antagonist therapy, the patient should be referred for further evaluation. For appropriate measure of the **ARR**, medication should be changed to drugs that have minimal effect on ARR (calcium channel blockers, hydralazine, doxazosin) for 4-6 weeks, hypokalemia if present should be corrected with K⁺ supplements. The blood should be collected in the mid-morning, at least 2 h after awakening and with the patient sitting 5-15 min.¹ The cutoff level considered to be a positive ARR is 30 (ng/dl/ng/[ml⁻¹ × h⁻¹]) (830 pmol/l per ng/[ml⁻¹ × h⁻¹]), together with an aldosterone level >10 ng/dl. A high ARR is also seen in chronic renal disease, where high potassium stimulates aldosterone release and in the case of rare genetic mutations leading to increased aldosterone levels. The **intravenous saline loading test** (2 L of IV saline are infused over 4h) or the less reliable **captopril challenge test** in patients with a contraindication to acute volume expansion are also used for confirmation.^{21, 27} **CT, magnetic resonance imaging** or isotopic techniques using radio labelled cholesterol are used for imaging of the adrenals. **Adrenal venous sampling** may be necessary to avoid false positive results that could provoke unnecessary adrenalectomy for non-functioning tumors.

Therapy

Includes medical therapy with mineralocorticoid receptor antagonists and laparoscopic adrenalectomy for patients with unilateral adenomas. Aldosterone synthetase inhibitors are under study.²⁶

Genetic testing

Genetic testing for familial forms of is indicated in patients with primary aldosteronism diagnosed at a young age (i.e., age <30 years) particularly if they have a family history of stroke at young age.²⁶

Phaeochromocytoma

It is a very rare cause of secondary hypertension (0.2–0.4%), inherited or acquired, with an estimated annual incidence of 2–8/million population.^{28 29} Susceptibility genes have been identified.³⁰ Pheochromocytomas are mostly benign catecholamine-producing tumors of chromaffin cells of the adrenal medulla or of a paraganglion. Typical clinical manifestations are sustained or paroxysmal hypertension, palpitations, pallor, pounding headaches, and sweating. However, their presentation is highly variable (hypertension occurs in about 70% of all cases of phaeochromocytoma) and can mimic many other diseases. If remaining unrecognized or untreated, it can be a life-threatening condition. Pheochromocytoma may be also associated with catecholamine-induced cardiac toxicity. This is characterized by myocardial inflammation, myocyte necrosis, and fibrosis that can lead to systolic and diastolic dysfunction.³¹

Diagnosis

The test with the highest sensitivity is the measurement of **plasma free metanephrines** (Table 4). However, because measurement of plasma free metanephrines is not widely available for routine diagnosis, measurement of **plasma** or **24-hour urinary fractionated metanephrines** and **catecholamines** remain the diagnostic test of choice.^{28 29} An increase in plasma fractionated metanephrines (metanephrine and normetanephrine) has a mean sensitivity of 97% and a specificity of 93% across 15 studies. In contrast, measurement of fractionated catecholamines (epinephrine, norepinephrine, and dopamine) is less sensitive, but clearly elevated values (>2 times the upper limit of the normal range) are also diagnostic.³⁰ However, mild elevations in the levels of fractionated metanephrines and catecholamines in plasma and urine are common in persons who do not have pheochromocytoma. Medications (e.g., tricyclic antidepressants, antipsychotic agents, serotonin-reuptake or norepinephrine-reuptake inhibitors, and levodopa) could cause elevations in endogenous catecholamines, and clinical circumstances (e.g., acute illness) could lead to false positive test results. To effectively screen for catecholamine-secreting tumors, tricyclic antidepressants and other psychoactive

agents should be tapered and discontinued at least 2 weeks before any hormonal assessments are performed.³⁰

Beta blockers and diuretics should be stopped before sampling. Stimulation or suppression tests with glucagon or clonidine, respectively, are less often used nowadays. Pheochromocytomas are localized by a computed tomography scan and magnetic resonance imaging of the adrenal glands and abdomen. Complementary ***123I-metaiodobenzylguanidine scintigraphy*** and ***18F-dihydroxyphenylalanine-positron emission tomography*** may also be useful. Because approximately 25% of pheochromocytomas are hereditary (multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), neurofibromatosis type 1, and familial paragangliomas), screening for genetic alterations is important. To date, mutations in several genes have been described leading to familial disorders associated with pheochromocytomas.³²

Therapy

Laparoscopic and adrenal sparing surgical intervention following preoperative alpha-blockade (*prazosin or phenoxybenzamine*) and fluid expansion is the treatment of choice and usually curative. In malignant pheochromocytomas, radiotherapy and chemotherapy are palliative treatment options.

Adrenal “Incidentaloma”

An adrenal “incidentaloma” is an adrenal mass, generally 1 cm or more in diameter, that is discovered serendipitously during a radiologic examination performed for indications other than an evaluation for adrenal disease.³³

The majority of adrenal incidentalomas are clinically nonhypersecreting, benign adrenocortical adenomas, occurring in 4-6% in the general population and in up to 70% of patients aged >70 years.³³ Other diagnoses include cortisol secreting adrenocortical adenoma (5%), pheochromocytoma (5%), adrenocortical carcinoma (5%) metastatic carcinoma (2.5%), and aldosterone secreting adenoma (1%). When adrenal masses occur bilaterally (15% of patients with adrenal incidentaloma), the most likely diagnoses are metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas, and infiltrative disease of the adrenal glands. Hormone production is determined by overnight ***dexamethasone suppression and blood or 24-h urinary fractionated metanephrines and catecholamines***, and ***CT scan*** is performed. Laparoscopic adrenalectomy is indicated if the adrenal mass is ≥ 4 cm in diameter, if the mass enlarges by 1 cm or more during a period of 4 years with 6-monthly examinations, or if evidence of autonomous hormonal secretion develops, laparoscopic adrenalectomy is considered.^{28, 33}

Other Causes of Hypertension

Cushing's syndrome, coarctation of the aorta, hypo- and hyperthyroidism, intracranial tumors, and drug-induced hypertension are also causes of secondary hypertension.

Although non-steroidal anti-inflammatory agents are the most common cause of drug-induced hypertension, other drugs as described in Table 1 should be also considered. Antiangiogenic and anti-vascular endothelial growth factor (VEGF) chemotherapy agents that are currently used for the treatment of various forms of cancer are a common cause of secondary hypertension.³⁴

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