Adrenal hypersecretion

Abstract

Hypersecretion from the adrenal glands is associated with hypertension. Causes include Conn syndrome, Cushing syndrome and pheochromocytoma. This article discusses their clinical features, diagnosis and treatment as well as the management of incidentally identified adrenal tumours (incidentaloma).

Primary aldosteronism (Conn syndrome)

Primary aldosteronism is due to over-production of aldosterone either from a solitary adenoma or from adrenal hyperplasia (table 1). The symptoms are non-specific and mostly due to hypokalaemia. They include muscle weakness, cramps, paraesthesiae, polyuria, metabolic alkalosis, suppressed renin activity and hypertension.

Aldosterone-producing adenomas are usually associated with hypertension with or without hypokalaemia. Primary aldosteronism may account for about 10-14% in the "essential hypertensive" labelled population, and is most often diagnosed in middle-aged adults (mean age at diagnosis, 42 years). It seems to be more common in women (64%) than in men.

Patients with severe or multidrug-resistant (>3 agents) hypertension without an obvious secondary cause, spontaneous or inappropriate hypokalaemia while taking conventional doses of diuretics, and those requiring excessive potassium supplementation should be screened for primary aldosteronism.

Plasma aldosterone concentration (PAC): plasma renin activity (PRA) ratio is widely accepted as the screening test of choice for primary aldosteronism (figure 1). In patients with suspected primary aldosteronism, screening can be accomplished by measuring a morning (preferably 0800 h) ambulatory paired random PAC and PRA. This test may be performed while the patient is taking antihypertensive medications and without posture stimulation. Spironolactone is the only medication that

will seriously interfere with interpretation of the ratio. A ratio of plasma aldosterone to plasma renin activity of 20 or more (measured while the patient is upright) and a PAC >15 ng/dl should prompt further testing. A ratio of >70, PAC >15 ng/dl and PRA <1.0 ng/ml per hour are virtually diagnostic of primary aldosteronism. Figure 1 is an algorithm for the laboratory diagnosis.

Treatment

Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with aldosterone producing adenoma (APA) or unilateral hyperplasia. Typically, the hypertension resolves in 1-3 months post-operatively. Idiopathic hyperplasia (IHA) and glucocorticoid remediable aldosteronism (GRA) should be treated medically. In addition, APA patients who are not fit for surgery require medical treatment. Spironolactone is the drug of choice to treat primary aldosteronism. Treatment goals are normotension and normokalaemia without potassium supplementation. Eplerenone, a new steroid-based anti-mineralocorticoid, which acts as a competitive and selective aldosterone receptor antagonist, may prove useful. In patients intolerant of aldosterone receptor antagonists, amiloride may be used for its potassium-sparing properties. However, amiloride lacks the mineralocorticoid receptor antagonist benefits. In addition, amiloride is not a very effective antihypertensive agent in patients with primary aldosteronism, and if hypertension persists, a second-step agent (eg. a thiazide diuretic) should be added.

Cushing syndrome

Endogenous Cushing syndrome (CS) results from chronic exposure to excess glucocorticoids produced by the adrenal cortex. It may be caused by excess ACTH production (80-85%), usually by a pituitary corticotroph adenoma (Cushing disease (CD)), less frequently by an extrapituitary tumour (ectopic ACTH syndrome), or very rarely by a tumour secreting CRH (ectopic CRH syndrome). CS can also be ACTH-independent (15-20%) when it results from excess secretion of cortisol by unilateral adrenocortical tumours, either benign or malignant, or by bilateral adrenal hyperplasia or dysplasia.

The suspicion of CS in a patient clearly arises in the presence of clinical features suggestive of CS (table 2). The clinical picture is not always florid, and suspicion should also arise with a less complete picture, particularly if concomitant recent weight gain, impaired glucose tolerance, and high blood pressure are present.

There are many clinical situations that can mimic CS-pseudo-Cushing states. These include psychiatric

Table 1. Forms of primary aldosteronism

- Aldosterone-producing adenoma (APA)
- Bilateral idiopathic hyperplasia (IHA)
- Primary (unilateral) adrenal hyperplasia (PAH)
- Aldosterone-producing adrenocortical carcinoma
- Familial hyperaldosteronism (FH)
 - FH type I (Glucocorticoid-remediable aldosteronism GRA)
 - FH type II (APA or IHA)

Diagnostic algorithm for primary hyperaldosteronism. This algorithm suggests tests that are used for screening, confirmation, and localization of aldosterone-producing tumours. To convert aldosterone values to pmol/L, multiply by 27.744; to convert urinary aldosterone excretion to nmol/d, multiply by 2.774; to convert 18-hydroxycorticosterone values to nmol/L, multiply by 0.0276. If there is more than one item, follow the respective numbers throughout the algorithm. CT - computed tomography; MRI - magnetic resonance imaging.

Figure 1. Diagnostic algorithm for primary aldosteronism

disorders (eg. depression, anxiety, obsessive-compulsive disorders), morbid obesity, poorly controlled diabetes mellitus, alcoholism and pregnancy.

Diagnosis

A stepwise approach is recommended. This includes tests for confirmation of CS, tests to diagnose a specific cause and tests for localisation of the site of excessive glucocorticoid production. Figure 2 is an algorithm for the laboratory diagnosis of patients with suspected Cushing syndrome.

An overnight 1mg dexamethasone suppression test or 24-hour urine free cortisol test should be the initial investigation. Choose another test or repeat the initial test at intervals if testing does not confirm CS. Further testing to exclude pseudo-Cushing states (obesity, alcoholism, depression and chronic stress) should be considered before obtaining more sophisticated localising tests if initial laboratory testing confirms mild-to-moderate hypercortisolism. Tests such as the dexamethasone-CRH suppression test or measurement of midnight cortisol level are useful in excluding pseudo-Cushing states.

Treatment of CS

Trans-sphenoidal exploration with selective excision of an ACTH-producing tumour is the treatment for CD. The cure rate is 80-90%. Incompletely resected tumours may require conventional or stereotactic radiation therapy to achieve remission. Steroidogenesis inhibitors are also indicated as adjunctive agents to pituitary radiation therapy as it does not reduce ACTH (and hence cortisol) values immediately. Mitotane, metyrapone and ketoconazole decrease cortisol effectively in the setting of radiation therapy. Ketoconazole is better tolerated. Bilateral adrenalectomy may be considered in resistant cases but this can lead to adrenal insufficiency and sometimes progressive enlargement of the ACTH-secreting pituitary tumour (Nelson syndrome). Adrenal and ectopic ACTH tumours should be removed surgically

whenever feasible. Small cell carcinoma of the lung is best treated with combined chemotherapy and radiotherapy. After treatment of CS, patients will have secondary adrenal insufficiency for up to 1 year and must be given glucocorticoid replacement therapy in tapering doses until the suppressed pituitary-adrenal axis recovers. Bisphosphonates are indicated to prevent and reverse low bone density caused by hypercortisolism. Alendronate improves bone density and reduces the fracture rate in patients who receive exogenous glucocorticoids.

Criteria for biochemical assessment of remission

There is still no general agreement regarding the definition of apparent cure. Very low serum cortisol, below 1.8 µg/dl (50 nmol/l at 0900 h), within 2 weeks after surgery is probably the best index of remission. Cortisol is usually measured 5-14 days after surgery and at least 24 h after the last dose of hydrocortisone.

Other drug treatments for manifestations of hypercortisolism, such as for hypertension and hypokalaemia, may be required before therapy directed at hypercortisolism has become effective.

Phaeochromocytoma

Phaeochromocytoma is seen in 0.01% to 0.1% of patients with hypertension. It arises from adrenal medulla and sympathetic ganglia, and secretes adrenaline, nor-adrenaline and dopamine. Phaeochromocytomas follow the 'rule of 10s': about 10% are extra-adrenal, 10% are bilateral, 10% are familial, 10% are malignant, 10% are recurrent, 10% are incidentally discovered and 10% are non-syndromic. Phaeochromocytoma is associated with hypertension in 90% of cases but it is paroxysmal in about 50%. The classic triad of headache, sweating and palpitations is highly specific for phaeochromocytoma. Arrhythmias and catecholamine-associated cardiomyopathy are the important cardiac manifestations. Most intra-adrenal and all extra-adrenal tumours secrete

Table 2. Clinical features of Cushing syndrome

Symptoms	Signs	Biochemical abnormalities
Fatigue	Hypertension	Hyperglycaemia
Muscular weakness	Supraclavicular fat pad	Hypokalaemia
Weight gain	Buffalo hump	Alkalosis
Easy bruising	Facial plethora	Osteoporosis
Emotional lability	Ecchymoses	
Depression	Wide purple striae	
Decreased libido	Hirsutism	
Menstrual disturbances	Proximal muscle weakness

Figure 2. Diagnostic algorithm for Cushing syndrome

noradrenaline leading to vasoconstriction and hypertension, whereas adrenaline secreting tumours cause vasodilation and hypotension. Evaluating patients for phaeochromocytoma is indicated in certain situations (table 3).

Table 3. Evaluation of patients for phaeochromocytoma

Refractory hypertension
Hypertension, accompanied by hyperadrenergic spells with: <ul style="list-style-type: none"> • nonexertional palpitations • sweating • headache • tremor • pallor
Family history of familial phaeochromocytoma
A genetic syndrome that increases the risk of phaeochromocytoma, such as: <ul style="list-style-type: none"> • multiple endocrine neoplasia type 2 • von Hippel-Lindau disease • neurofibromatosis type 1
History of gastric stromal tumour or pulmonary chondromas (Carney triad)
An incidentally discovered adrenal mass

Diagnosis

Confirmatory testing is best done following a paroxysm. Measurement of fractionated metanephrines, catecholamines and vanillylmandelic acid in a 24-hour urine collection has been the traditional test. However, plasma free metanephrines should be the investigation of choice as they are constantly produced by leakage of catecholamines from the tumour and elevated levels of plasma free metanephrines have >99% sensitivity and >89% specificity for phaeochromocytoma. Equivocal test results require a clonidine suppression test. This test differentiates centrally mediated catecholamines from those produced by a tumour. Once the diagnosis is confirmed, the localisation is best done with CT-scan and T2 weighted MRI. Additional imaging with meta-iodobenzylguanidine (MIBG) scintigraphy, MRI skull base to pelvis, and positron emission tomography are required to locate extra-adrenal tumours.

Treatment

Laparoscopic adrenalectomy is the best treatment. Proper peri-operative preparation is mandatory. As patients are hypovolaemic, volume expansion is achieved by

isotonic saline and alpha-blockers, preferably phenoxybenzamine. A beta-blocker can be added to control reflex tachycardia only after euvoemia has been achieved. In patients with malignant or unresectable disease, treatment with tumour-directed therapy should be considered.

Follow up

Clinical and laboratory measures are used postoperatively to document curative resection. Blood pressure measurements should be done daily for the first 2 weeks after surgery. A 24-hour urine collection for catecholamines and metanephrines 1 to 2 weeks after surgery is necessary. If a bilateral adrenalectomy is performed, lifelong glucocorticoid and mineralocorticoid replacement therapy is mandatory.

24-hour urinary excretion of metanephrines and catecholamines or plasma metanephrines should be checked annually for at least 10 years as surveillance for tumour recurrence in the adrenal bed, metastatic disease or delayed appearance of multiple primary tumours.

Adrenal incidentalomas

An incidentally discovered adrenal mass is termed an 'incidentaloma'. All patients with an incidentaloma should have a 1mg dexamethasone suppression test and a measurement of free metanephrines in plasma. Patients with hypertension should also undergo measurement of serum potassium and plasma aldosterone concentration/plasma renin activity ratio. A homogeneous mass with a low attenuation value (less than 10 HU) on CT scan is probably a benign adenoma. Surgery should be considered in all patients with functional adrenal cortical tumours that are clinically apparent. All patients with biochemical evidence of phaeochromocytoma should undergo surgery. Data are insufficient to indicate the approach to managing patients with subclinical hyperfunctioning adrenal cortical adenomas. Patients with tumours greater than 6 cm are usually treated surgically, whereas those with tumours less than 4 cm are monitored. In patients with tumours between 4 and 6 cm, additional criteria should be considered in making a decision. Either open or laparoscopic adrenalectomy is acceptable for resection of an adrenal mass. The choice of procedure will depend upon the likelihood of an invasive adrenal cortical carcinoma, technical issues, and the experience of the surgical team. Further follow up may not be warranted in patients with tumours that remain stable on two imaging studies carried out at least 6 months apart and do not show hormonal hypersecretion for 4 years.

Further reading

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