Conn’s syndrome (primary hyperaldosteronism)

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Definition First described in 1957 in a patient with hypertension and low serum potassium, primary hyperaldosteronism (PA) now comprises a heterogeneous group of disorders characterised by hypertension and inappropriately raised plasma aldosterone concentrations. It is of importance not only because, if left untreated, it can lead to cardiovascular and renal complica tions, but also because a significant proportion of patients can be improved or cured with surgery . Incidence PA is the most common cause of endocrine hypertension and may be present in up to one-fifth of patients investigated for hypertension. It is twice as common in females as in males and its prevalence increases significantly in those with drug-resistant hypertension. About 30–40% of cases are due to an aldosterone producing adenoma (APA) of the cortex and just over one-third of patients will have hypokalaemia at presentation. Pathology Although Conn originally described a patient with an APA, PA may also be due to bilateral adrenal hyperplasia, adreno cortical carcinoma (ACC), unilateral hyperplasia and familial hyperaldosteronism (FH). Determining the underlying cause is key because this will determine the most appropriate treatment modality (surgery versus medical therapy). In all its forms, PA is characterised by volume expansion secondary to sodium retention and the variable occurrence of hypokalaemia due to increased potassium excretion into the renal tubule. Resultant hypertension leads to an increased risk of cardiovascular morbidity (stroke, myocardial infarction and atrial fibrillation) and mortality compared with matched controls. Further more, glucose intolerance, type 2 diabetes and the metabolic syndrome are also more common in those with PA. Aldosterone-producing adenoma Arising in the zona glomerulosa, these tumours are typically between 10 and 20 /uni00A0 mm in maximal diameter at presentation, well circumscribed and macroscopically golden yellow on slicing (the ‘canary tumour’). Ninety per cent contain somatic mutations; although these may be associated with certain clinical features, their presence does not yet a ff ect clinical management. The most common mutations are those of the potassium channel encoded by the KCNJ5 gene; these are pres ent in approximately 40% of patients with APA. Mutations are thought to trigger calcium influx into glomerulosa cells, resulting in aldosterone secretion and cellular proliferation. Phenotypically , they are more prevalent in females and ar associated with larger tumours and higher aldosterone levels, but are not associated with adrenal hyperplasia. In contrast, less common variants, including somatic mutations in the Jerome William Conn , 1907–1981, Professor of Internal Medicine, University of Michigan, Ann Arbor, MI, USA. stronger male preponderance. Bilateral adrenal hyperplasia (idiopathic hyperplasia) Traditionally thought to result from di ff use hyperplasia of the zona glomerulosa, the pathophysiology of bilateral adrenal hyperplasia and its drivers remain poorly understood. More recently , aldosterone-producing cell clusters with a high prev - alence of somatic mutations in the CACNA1D l-type calcium channel gene have been identified in the adrenal cortex

of patients with bilateral hyperplasia and these ‘micro-APAs’ have been cited as the putative cause. - Familial hyperaldosteronism types I–IV These rare genetic variants of PA are all inherited in an autosomal dominant fashion (50:50 chance that o ff spring of an a ff ected individual will inherit the disorder). FH type I or glucocorticoid-remediable aldosteronism (GRA) arises as a result of a CYP11B1 / CYP11B2 chimeric gene and presents with (typically normokalaemic) hypertension when the patient is in their early twenties. The chimeric gene - leads to ACTH-dependent aldosterone secretion and is treated by administering physiological doses of glucocorticoids, which suppress ACTH release. Thus treatment is always medical. FH types II–IV (caused by germline CLCN2 pathogenic variants, KCNJ5 pathogenic variants and CACNA1H patho - genic variants, respectively) all result in early-onset PA within a ff ected kindreds. Type II FH may lead to APAs or bilateral - adrenal hyperplasia; type III massive bilateral adrenal hyper - plasia; and type IV developmental disorder with bilateral adrenal hyperplasia. Genetic testing for these disorders is in evolution and, currently , it is recommended that treatment should be as for pa tients with sporadic PA. Clinical presentation Aside from hypertension, patients may be asymptomatic unless they are hypokalaemic, in which case muscle weakness, cramps and fatigue may be present. Hypokalaemia-induced palpita - - tions after initiation of diuretic therapy or polyuria and poly - dipsia from nephrogenic diabetes insipidus are also described. Physical signs include hypertension, associated bruits and retinopathy . It is worth noting that the following presentations might also warrant scr eening for PA: drug-resistant hyperten - sion, hypertension and obstructive sleep apnoea, hypertension with incidentaloma, patients with first-degree relatives with PA, and a family history of early-onset hypertension or stroke. Diagnosis Biochemical Although routine tests may reveal hypokalaemia and/or - metabolic alkalosis, the diagnosis depends on the presence of non-suppressed plasma aldosterone (pmol/L) and a suppressed plasma renin activity (nmol/L/h). The two are combined to give a plasma ARR: if >850 this is suggestive of PA; if >1700 e it is very likely to be PA. Because most, if not all, patients will be prescribed antihypertensives, it is important to stop agents that might interfere with interpretation of the ARR. Although the renin–angiotensin system, i.e. ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors and aldosterone antagonists (spironolactone and eplerenone), should be stopped for 2 weeks beforehand. More severe biochemical disease is more likely to be due to an APA. Radiological Once a biochemical diagnosis is secure, the primary objective is to determine whether it is due to a unilateral APA (or, rarely , carcinoma) or bilateral hyperplasia. High-resolution (2- to 3-mm slices) adrenal CT is the initial investigation of choice and APAs typically appear as a hypodense (<10 /uni00A0 HU) unilateral 1- to 2-cm adrenal nodule; carcinomas are heterogenous and >60 /uni00A0 mm; and bilateral hyperplasia presents as bilateral bulky adrenal enlargement. Diagnosis of a unilateral APA on CT alone is controversial: tumours are often small and this, combined with the increas ing preponderance for adrenal nodules with advancing age, means that a missed contralateral nodule could be the underly ing cause. For this r eason, adrenal vein sampling (A VS) is con sidered the gold standard for confirming unilateral secretion. Sur gery based on biochemistry and a unilateral adrenal lesion on imaging alone is e ff ective in those younger than 35 years, leaving A VS for patients older than 35 years or with neg 11 imaging or bilateral nodules. PET scanning with C-metomi date, an 11 β − hydroxylase (CYP11B1) and aldosterone syn thase (CYP11B2) inhibitor, has been compared with A VS and found to be 86% specific and 76% sensitive for lateralising PA; it is therefore a useful adjunct in patients with failed or equivo cal A VS results (Figure 57.3) (see Further r eading). Treatment Medical Prior to surgery , hypertension and hypokalaemia should be adequately corrected. The preoperative response to aldoste rone receptor antagonist

(spironolactone/eplerenone) therapy is a useful surrogate for predicting likely success. In general, the shorter the time to diagnosis, the better the likely outcome from surgery . Surgical Unilateral APA should be managed by minimally invasive adrenalectomy , which results in resolution of hypertension and hypokalaemia or a reduction in antihypertensive requirement in the vast majority of patients. Bilateral disease Unless hyperplasia is marked, with dominant nodules >40 /uni00A0 mm that are indeterminate, patients with bilateral disease should be managed medically with aldosterone antagonists and other antihypertensives. If this is unsuccessful, lateralising investigations may be used to determine if one side is dominant, in which case excision of that side may improve medical control. Familial hyperaldosteronism These disorders are extremely rare and are best managed in a multidisciplinary fashion in conjunction with tertiary - - - ative - - - -

(b) (c) Figure 57.3 A patient with con /f_i rmed Conn’s syndrome. Magnetic resonance imaging (a) failed to demonstrate a lesion but a 30-SUV

11 max lesion was demonstrated on a C-metomidate positron emission tomography (PET)–computed tomography (CT) scan (b) . (c) Surgical specimen sliced to reveal a 6-mm

aldosterone-producing adenoma in the medial limb. The patient’s hypertension resolved with laparo

scopic left adrenalectomy (PET-CT image courtesy of Mark Gurnell, Addenbrooke’s Hospital, Cambridge). SUVmax, maximum standard unit value.

if a unilateral secreting lesion is found to be the cause.

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