57 T_h e adrenal glands and other abdominal endocrine disorders

- Treatment

ADRENAL HAEMORRHAGE

ADRENAL HAEMORRHAGE

Definition Adrenal haemorrhage is a serious condition that can result in adrenal insu ffi ciency , shock, acute adrenal crisis and mortality if not managed with adequate treatment. The adrenal glands are, per weight of tissue, one of the most vascular tissues in the body . A number of factors predispose to haemorrhage, includ - ing infection (sepsis), myocardial infarction, anticoagulants, trauma, surgery and antiphospholipid syndrome. Clinical presentation can vary from non-specific abdominal pain to adrenal insu ffi ciency or hypovolaemic shock. Investigation CT scanning is the most common way to diagnose the condi - tion (Figure 57.9a). - Management Most adrenal bleeds are successfully managed conservatively . Anticoagulation therapy should be stopped temporarily . Rarely , interventional radiology may be necessary to staunch the bleed (Figure 57.9b). In cases of bilateral haemorrhage, the possibility of adrenal insu ffi ciency should be considered. - -

ADRENAL INSUFFICIENCY

ADRENAL INSUFFICIENCY

Adrenal insu ffi ciency may be primary , secondary or tertiary . Primary insu ffi ciency (Addison’s disease) is due to adreno - cortical disease, whereas secondary and tertiary insu ffi ciency arise from pituitary and hypothalamic pathology , respectively . Addison’s disease most commonly occurs when there is auto - immune (70–90%) or tuberculous destruction of the adrenal cortex and results in glucocorticoid and mineralocorticoid en insu ffi ciency . This is in contrast to secondary disease (lack of ACTH) and tertiary disease (lack of CRH secretion), wher e th, UK, described this syndrome in 1911. e his account of the syndrome in 1918.

Type of AI Primary AI a Secondary AI Tertiary AI

tion (under control of the renin–angiotensin system) is spared. The causes are summarised in Table 57.1 .

ANATOMY Adrenal glands

ANATOMY Adrenal glands

The weight of a normal adrenal gland is approximately 4 /uni00A0 g. The adrenal glands are paired and situated in the retroperi - - toneum, near the upper poles of the kidneys, within Gerota’s - capsule. They are not symmetrical. The right adrenal gland is located between the right liver lobe and the diaphragm, close to and partly behind the inferior vena ca va (IVC). The left - adrenal gland lies superior–medial to the upper pole of the left kidney and the renal pedicle. It is covered by the pancreatic tail and the spleen (Figure 57.1). Each adrenal gland is supplied by multiple small arterial branches from three main vessels: the aorta, the inferior phrenic artery and the renal artery . A usually - single large adrenal vein drains into the IVC on the right side and into the renal vein on the left side.

Figure 57.1 Anatomy of the adrenal glands.

Acute adrenal insufficiency (adrenal or Addisonian crisis)

Acute adrenal insufficiency (adrenal or Addisonian crisis)

This is a medical emergency . Owing to its non-specific features (shock with some or all of the following: fever, nausea, vomiting, abdominal pain, hypoglycaemia and electrolyte imbalance), it can be di ffi cult to diagnose. It is also rapidly fatal unless prompt and appropriate treatment is instituted early in its course. Typically there is a precipitating illness that may unmask longstanding adrenal insu ffi ciency or a history of trauma or severe sepsis that result in adrenal haemorrhage or infarction (Waterhouse–Friderichsen syndrome), respectively . Because intestinal symptoms and fever are frequent, Addisonian crisis may often be misdiagnosed as an acute abdominal emergency .

Adrenocortical carcinoma

Adrenocortical carcinoma

Definition ACC is a rare aggressive malignancy that arises from the adrenal cortex. The prognosis is variable but is generally poor, in part owing to its tendency to present at a late stage. Although most ACCs are sporadic, a minority occur as part of genetic tumour syndromes such as multiple endocrine neoplasia type 1 (MEN /uni00A0 1), familial adenomatous polyposis and the Li–Fraumeni and Lynch syndromes. Optimal surgery remains the best way of curing the patient and so preoperative diagnosis and planning are key in ensuring this outcome. Incidence Estimated incidence is one or two cases per 1 000 000 popu lation per year and, in keeping with benign adrenocortical tumours, a female predominance is observed (1.5:1). Don H Nelson , 1925–2010, Professor of Medicine, University of Utah, Salt Lake City , UT , USA Frederick Pei Li , 1940–2015, Professor of Clinical Cancer Epidemiology , Harvard, USA Joseph F Fraumeni Jr , b. 1933, Director of the National Cancer Institute Henry T Lynch , 1928–2019, Professor of Cancer Research, Creighton University School of Medicine, Omaha, NE, USA. Lawrence M Weiss , contemporary , pathologist, Aliso Viejo, Ca, USA. fourth and fifth decades. Pathology Tumours are often large (>10 /uni00A0 cm) with a cut surface that ranges - from orange to brown (Figure 57.7). Necrosis is usually present. Distinguishing between benign and malignant adrenocortical tumours may be di ffi cult, with the presence of local invasion or - distant metastasis being the only definitive criteria. If neither are present, the modified Weiss histopathological system may be used to guide management. It comprises five criteria: >6 mitoses/50 high-power fields, ≤ 25% clear tumour cells in cytoplasm, abnormal mitoses, necrosis and capsular invasion. If a criterion is absent, it is scored 0; if present, it scores 2 for the first two criteria and 1 each for the last three. A total score ≥ 3 is suggestive of malignant behaviour. More recently the use of the Ki-67 proliferation index has been advocated, with increasing count suggesting poorer prognosis. Clinical presentation Patients may present with hormonal excess (50–60%) or symptoms of an abdominal mass such as abdominal or back pain (30–40%). Around one in six ACCs present as adrenal incidentalomas. Those that are hormonally active usually cause Cushing’s syndrome or a mixed picture of Cushing’s and virilisation in women. Mineralocorticoid excess is rare, as is feminisation in male patients. Diagnosis Although radiological investigations are critical in diagnosis, the presence of autonomous secretion of glucocorticoids, sex hormones and steroid precursors should also be carefully evaluated. Phaeochromocytoma (PCC) must also be excluded. - , MD, USA.

Figure 57.7 Adrenocortical carcinoma that caused Cushing’s

syn

drome and virilisation in a female patient.

Radiology ACC is often readily diagnosed on CT or MRI (Figure 57.8 where size (>6 /uni00A0 cm), heterogeneous appearance and presence of necrosis are suggestive and local invasion and metastatic disease are diagnostic. Common sites of metastases are the lungs and liver, so staging should include the thorax. FDG-PET scanning is complementary and is advised to exclude occult metastatic disease in suspicious lesions. A maximum standard unit value (SUVmax) >40 or 1.5 times higher than the liver 11 both suggest malignant tumours. The use of C-metomidate PET may improve diagnostic accuracy but is not widely avail able. In terms of tissue diagnosis, adrenal biopsy is discouraged and fine-needle aspiration cannot distinguish benign from malignant tumours. Biopsy may have a role in patients with widespread metastatic disease at presentation to guide pallia tive systemic trea tment. Biochemistry Glucocorticoid excess should be excluded by careful history and examination, followed by low-dose overnight DST . Serum levels of adrenal androgens (DHEAS, androstenedione, testosterone, 17-hydroxyprogesterone) and serum oestradiol in men and postmenopausal women should also be measured. In patients who are hypertensive, the aldosterone–renin ratio should be measured along with the serum potassium. Steroid precursors can be measured in 24-hour urine collections and may demonstrate a particular pattern on mass spectrometry although use is not widespread at present. Lastly , 24-hour urine or plasma metanephrines should be measured in all patients to exclude PCC. Treatment Surgery Successful R0 resection of the tumour should be the aim of surgery and o ff ers the best chance of cure for the patient. Preoperative assessment should therefore focus on determin ing whether any adrenal tumour is potentially malignant as this will guide the operative strategy . Treatment should take treating this rare disease. Patients with cortisol excess should be given perioperative hydrocortisone. At presentation, ther e are three common scenarios: /uni25CF Indeterminate or probably malignant tumour <6 /uni00A0 cm : laparoscopic adrenalectomy may be feasible in this situation, but if there is evidence of local invasion on imaging or suspicion of it at laparoscopy open surgery is mandated. /uni25CF Indeterminate or probably malignant tumour >6 /uni00A0 cm : laparoscopic surgery is not advised. In this scenar - io open radical resection must be undertaken, if necessary en bloc with involved adjacent organs (see Surgery of the adrenal glands). /uni25CF Indeterminate or probably malignant tumour <6 /uni00A0 cm with synchronous metastatic disease . For limited metastatic disease , open resection of the tumour and intra-abdominal metastases is advised. For distant disease, resection of the primary followed by adjuvant systemic or surgical treatment of metastases is appropriate. For widespread metastatic disease , initial surgery is), no longer routinely advised. Instead, palliative treatment with mitotane with or without chemotherapy should be pursued. If there is significant disease regression after 3–6 months, surgery may then become an option. More rarely , patients present with locally advanced disease with tumour extension into the great vessels. In this situation, it is recommended that such patients are referred to centres with experience of treating these cases. - Oncological treatment Patients at high risk of recurrence (size >5 /uni00A0 cm, Ki-67 >10%, tumour rupture at surgery , tumour thrombus) and those with metastatic disease should commence mitotane therapy as soon - as possible (for up to 5 years) as this has been shown to improve disease-free and overall survival. Palliative EDP (etoposide– doxorubicin–cisplatin) chemotherapy may also be an option if there is disease

progression despite mitotane therapy . Unless there is ongoing steroid excess, all patients treated with mito - tane should receive oral hydrocortisone replacement therapy . According to the European Network for the Study of Adrenal Tumours (ENSAT) classification, the 5-year, disease - specific survival rates for ACC are: 82% in stage I (tumour <5 /uni00A0 cm; T1N0M0), 61% in stage II (tumour size >5 /uni00A0 cm; T2N0M0), 50% for stage III (tumour of any size with at least one of the following factors: tumour infiltration in surrounding tissues [T3], tumour invasion into tumour thr ombus in the vena cava or renal vein [T4], positive lymph nodes [N1] but no distant metastases) and 13% for stage IV (distant metastases) (see Further reading).

Figure 57.8 Magnetic resonance imaging of adrenocortical carcinoma (arrow) in a patient with cortisol and testosterone excess.

Chronic adrenal insufficiency

Chronic adrenal insufficiency

Patients with chronic adrenal insu ffi ciency may also be di ffi cult to diagnose because symptoms appear insidiously over time. They may experience anorexia, weakness and nausea and, in the case of primary adrenal insu ffi ciency , hyperpigmentation of the skin and oral mucosa because of the loss of negative feedback on secretion of ACTH and POMC. Hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia are commonly observed due to the deficiency of mineralocorti coids. Diagnosis The diagnosis of adrenal insu ffi ciency relies on demonstrating cortisol deficiency and then determining whether this is ACTH dependent or independent by performing an ACTH stimula tion test (synacthen test). Blood is drawn for basal ACTH and cortisol. If both are low , the diagnosis is secondary or tertiary adrenal insu ffi ciency . If the ACTH is high and the cortisol is low , the cause is adrenal disease (primary adrenal insu ffi ciency). Synacthen testing is used because it is the quickest way to deter mine if there is any adrenal function; adrenal function is present for some after the onset of pituitary or hypothalamic disease, whereas there will be no response w hen the adrenal glands are diseased. Treatment If acute adrenal insu ffi ciency is suspected, treatment must be commenced immediately while the results of confirmatory testing are awaited. Blood should be drawn for plasma ACTH, serum cortisol, plasma renin activity and aldosterone and therapy with intravenous saline and hydrocortisone should be commenced. A typical regime would consist of a 100-mg bolus of intravenous hydrocortisone followed by 50 /uni00A0 mg intra venous hydrocortisone 6-hourly and 2–3 litres of 0.9% saline in 6 hours, with careful cardiovascular monitoring to prevent fluid overload. Concomitant infections, which are frequently pr esent, should also be treated. Fluids and steroids are then tapered as the patient stabilises. therapy with daily oral hydrocortisone (15–25 /uni00A0 mg orally in two or three divided doses) and fludrocortisone (0.05–0.2 /uni00A0 mg each morning orally). Patients must be advised about the need to take lifelong glucocorticoid and mineralocorticoid replace - ment therapy . To prevent an Addisonian crisis, patients must be aware of the need to double the dose in cases of illness or stress (‘sickness day rules’). If patients with adrenal insuf - ficiency are scheduled for surgery , appr opriate steroid cover must be administered.

Congenital adrenal hyperplasia (adrenogenital syndrome)

Congenital adrenal hyperplasia (adrenogenital syndrome)

Virilisation and adrenal insu ffi ciency in children are pathog - nomonic of congenital adrenal hyperplasia (CAH). This is an autosomal recessive disorder caused by a variety of enzy - matic defects in the synthetic pathway of cortisol and other steroids from cholesterol. The most frequent defect (95%) is the 21-h ydroxylase deficiency , which has an incidence of 1 in 5000 live births. Excessiv e ACTH secretion secondary to the loss of cortisol leads to an increase in androgenic cortisol precursors and to CAH. CAH may present in girls at birth with - ambiguous genitalia or as late-onset disease at puberty . Hyper - tension and short stature, caused by the premature epiphyseal plate closure, are common signs. A ff ected patients are treated by replacement of hydr ocortisone and fludrocortisone. Large hyperplastic adrenals may need to be removed if symptomatic.

Conn’s syndrome (primary hyperaldosteronism)

Conn’s syndrome (primary hyperaldosteronism)

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.

Cushing’s syndrome

Cushing’s syndrome

Definition Hypercortisolism may arise as a result of excess ACTH secretion (termed pituitary dependent; Cushing’s disease), ectopic ACTH secretion from a non-pituitary tumour, exogenous corticosteroid therapy or autonomous secretion of endogenous glucocorticoids from cortical tumours of the adrenal glands (pituitary independent; Cushing’s syndrome). ACTH-secreting pituitary tumours account for 70–80% of cases, whereas ectopic ACTH production from foregut neuro endocrine tumours and small cell lung tumours are the cause in 10%. In the remaining 10–15%, Cushing’s syndrome arises from unilateral cortisol-secreting adenomas and occasionally ACCs or bilateral nodular adrenal hyperplasia. Left untreated, hypercortisolism leads to a fivefold increase in the risk of dea from cardiovascular disease. The principal aim therefore is to determine and treat the underlying cause, while avoiding, if possible, long-term hormonal deficiency or dependence on medication. Incidence Iatrogenic Cushing’s syndrome is likely to be most prevalent as a result of the widespread use of corticosteroids for other diseases but this is poorly documented. The incidence of pituitary-dependent disease is around six or seven per million per year, whereas the incidence of ectopic ACTH syndrome is around one per million per year. Although adrenal tumours are extremely common, 99% do not present with endocrine disease and so adrenal Cushing’s syndrome is also quite uncommon (one or two per million per year). Both ACTH-dependent and -independent Cushing’s have a strong female preponderance (four to six times), whereas ectopic ACTH syndrome is twice as common in men. The incidence increases significantly from age 50. Pathology Similar to PA, the most common cause of adrenal Cushing’s (syndrome) is an adrenocortical adenoma, although it can arise in the setting of bilateral nodular hyperplasia or less commonly ACC (see Adrenocortical carcinoma). Adrenal adenoma Tumours are well circumscribed, nodular in appearance and composed of polygonal eosinophilic and lipidised cells in a nested pattern. The resulting hypercortisolism leads to suppressed ACTH, which causes atrophy of fasciculata and reticularis, not glomerulosa, in the residual or opposite adrenal gland. Primary bilateral macronodular adrenal hyperplasia Primary bilateral macronodular adrenal hyperplasia (BMAH) is a relatively uncommon cause of Cushing’s syndrome. It may present as bilateral adrenal incidentalomas and is characterised by the presence of bilateral non-pigmented adrenal nodules subclinical Cushing’s. Clinical presentation Because of the pleiotropic actions of cortisol, the clinical features of Cushing’s syndrome are broad and multisystem (Summary box 57.2). The typical patient is characterised by a facial plethora, a bu ff alo hump and a moon face in combina - tion with hypertension, diabetes, central obesity and proximal muscle-wasting, traditionally referred to as the ‘lemon on sticks’ appearance (Figures 57.4 and 57.5). Clinical signs can be minimal or absent in patients with subclinical Cushing’s syndrome. - Summary box 57.2 Clinical features of Cushing’s syndrome th Diagnosis Biochemical It is important to exclude iatrogenic Cushing’s due to ingested steroid therapy , including potent inhaled corticosteroids. Inves - tigations should then determine if hypercortisolism is present and whether it is ACTH dependent or independent. Imaging should not be pursued until the diagnosis is secure. Endocrine Society 2008 guidance states that two of the following tests should be abnormal for diagnosis:

/uni25CF late-night salivary cortisol (two measurements): raised levels signify a loss of diurnal rhythm; /uni25CF 24-hour urinary free cortisol (UFC) excretion (two mea - surements): more than three times the upper limit signifies overspill into the urine;

Clinical feature Incidence (%) Obesity 90 Hypertension 85 Facial plethora 70 Hirsutism 75 Glucose intolerance/diabetes 75 Hyperlipidaemia 70 Abdominal striae 50 Acne 35 Easy bruising 35 Osteoporosis 80 Proximal myopathy 65 Depression/mania/psychosis 85 Menstrual disorders 70 Decrease libido/impotence 85 Renal stones 50 Adapted from Raff H, Sharma ST, Nieman LK. Physiological basis for the etiology, diagnosis, and treatment of adrenal disorders: Cushing’s syndrome, adrenal insuf /f_i ciency, and congenital adrenal hyperplasia. Compr Physiol 2014; 4 : 739–69.

/uni25CF overnight 1-mg DST (dexamethasone suppression test): non-suppressed morning cortisol >50 /uni00A0 nmol/L; /uni25CF raised serum ACTH signifies pituitary-dependent dis ease; if it is adrenal in origin, the ACTH is suppressed (<5 /uni00A0 pg/mL). Radiological These tests should determine the causative lesion. The ACTH result will determine which diagnostic pathway is taken. /uni25CF ACTH raised : pituitary MRI and inferior petrosal sinus sampling to exclude pituitary microadenoma. If both are negative, this suggests ectopic ACTH syndrome, which warrants CT imaging of the thorax, abdomen and pelvis. adjunct and is 75–80% sensitive in confirming the source of ectopic ACTH. /uni25CF ACTH suppressed : dedicated adrenal CT or MRI to determine if unilateral adenoma or bilateral nodular hyperplasia (or rarely adrenocortical cancer) are present. Benign lesions are typically hypodense and <10 /uni00A0 HU on non-contrast CT .

Figure 57.4 A 34-year-old patient with Cushing’s syndrome whose symptoms included thickening of the face, weight gain and acne. Today patients with Cushing’s syndrome rarely have the full-blown appearance shown in older textbooks. Figure 57.5 Discrete central obesity, ecchymosis and fragile skin in a patient with Cushing’s syndrome.

EMBRYOLOGY

EMBRYOLOGY

There are two distinct functional units in the adrenal gland: cortex and medulla. The cortex is derived from the mesoderm. At about the fifth week of life the fetal cortex develops; this is subsequently surrounded by a second wave of mesothelial cells that will eventually form the definitive cortex. After birth the fetal cortex regresses except for its outermost layer, which di ff erentiates into the reticular zone. The adrenal medulla is derived from ectodermal chroma ffi n cells that are believed to have migrated from the neural crest. The adrenal cortex represents 90% of the gland and is arranged in a zonal configuration. The outer zona glomer ulosa contains small, compact cells loosely arranged in cords. The central zona fasciculata can be identified by larger, Emil Zuckerkandl , 1849–1910, Professor of Anatomy , Vienna, Austria the largest layer (70%). Compact and pigmented cells charac - terise the inner zona reticularis . The adrenal medulla is the inner core that consists of a thin layer of large chroma ffi n cells (stain yellow with chromium), which synthesise, store and secr ete catecholamines.

Extra-adrenal paraganglia

Extra-adrenal paraganglia

Paraganglia are neuroendocrine cells associated with the autonomic nervous system. They can be adrenal (medulla) or extra-adrenal. Extra-adrenal paraganglia occur throughout the sympathetic nervous system and along some branches of the parasympathetic glossopharyngeal and vagus nerves. There are four subgroups: 1 Sympathetic : the largest cluster is the organ of Zucker kandl, which is located at the aortic bifurcation or close to the origin of the inferior mesenteric artery . 2 Chemoreceptor : including aortic and carotid bodies that assist in the regulation of respiration. 3 Visceral–autonomic : in the urinary bladder and peripheral blood vessels. 4 Intravagal : situated within or adjacent to the vagal trunk. Neoplasms of extra-adrenal paraganglia are called para gangliomas (PGLs). Tumours of chemoreceptors are usually referred to as chemodectomas (see Chapter 52) and those from parasympathetic ganglia are termed glomus tumours.

INCIDENTALOMA

INCIDENTALOMA

Definition An asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease is termed an inciden taloma. The aetiology includes benign and malignant tumours of the cortex and medulla or of extra-adrenal origin. These tumours can be either non-functioning (silent) or functioning (secreting excess hormones). Incidence Autopsy studies suggest a prevalence of clinically inapparent adrenal masses of the order of 2%, which increases with age. Radiological incidentalomas are seen in about 3% of scans at the age of 50, rising to 10% in the elderly . Investigation Incidentaloma embraces all adrenal pathology and so the steps to management are described here and the detail for each pathology will follow in the individual sections of the chapter. A clear evidence-based algorithm for assessing patients with adrenal incidentaloma has been derived (Figure 57.2 The following should be assessed in parallel: Harvey Williams Cushing , 1869–1939, Professor of Surgery , Harvard University Medical School, Boston, MA, USA. Sir Godfrey Newbold Hounsfield , 1919–2004, British electrical engineer, won the 1979 Nobel Prize in Physiology or Medicine for helping to develop the diagnostic imaging technique known as X-ray computed tomography . Cushing’s syndrome and virilising tumours are associated with higher rates of malignancy (50% and 30%, respec - tively). The optimal way to determine malignancy is by means of a non-contrast computed tomography (CT) scan and measurement of the density of the lesion b y Hounsfield units (HU). Benign tumours are low density (≤ 10 /uni00A0 HU). In cases of uncertainty , consideration is given to fluorodeoxyglucose (FDG)–positron emission tomogra - - phy (PET) scanning, magnetic resonance imaging (MRI) with chemical shift or contrast CT and measurement of washout. Radiological findings suspicious of malignancy are shown in Summary box 57.1 . /uni25CF Is the tumour functionally active? This is deter - mined by: /uni25CF Clinical assessment /uni25CF 1 /uni00A0 mg overnight dexamethasone suppression test (DST) /uni25CF Measurement of plasma or urinary metanephrines /uni25CF Plasma aldosterone–renin ratio (ARR) /uni25CF Sex hormones and steroid precursors Summary box 57.1 Radiological features suspicious of adrenal malignancy /uni25CF). /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Management All patients should be discussed in a multidisciplinary setting. Small (<40 /uni00A0 mm), benign non-functioning tumours do not require surgery , but patients should undergo a follow-up CT/MRI at 6 months. There is no consensus about follow-up beyond that period. However, there is evidence that a tumour >30 /uni00A0 mm has an increased risk of developing hyperfunction over time. Adrenalectomy is the standard of care for patients with unilateral tumours causing hormone excess. Adrenalectomy is recommended for all tumours >40 /uni00A0 mm in diameter, tumours showing imaging characteristics of malignancy and tumours sho wing significant growth. Laparoscopic adrenalectomy is recommended for unilat - eral adrenal masses with radiological findings suspicious of malignancy and a diameter <60 /uni00A0 mm, but without evidence of local invasion. Open adrenalectomy is recommended for unilateral adrenal masses with radiological findings suspicious of malignancy . An individualised approac h is required for patients whose tumours fall outside the above categories.

Unilateral adrenal mass Radiological suspicion of malignancy No Yes Functioning Local tumour? invasion No Yes No Yes No surgery Laparoscopic Diameter Open adrenalectomy ≤ 6 cm? adrenalectomy No Individualised surgical approach Figure 57.2 Algorithm for the investigation of adrenal incidentaloma. (After Fassnacht M, Arlt W, Bancos I et al . Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2016; 175 (2): G1–G34.) Diameter >40 /uni00A0 mm and >10 /uni00A0 HU density Contrast-enhanced washout CT Relative <40% Absolute <60% MRI chemical shift: no change in signal intensity on out-of- phase imaging FDG-PET: positive uptake Yes

Introduction

INTRODUCTION

Two major systems are held responsible for the regulation of homeostasis of the human body: the endocrine and neuroen docrine systems. Both interact with their target organs or target tissues via secretion of ubiquitous messenger molecules, which can be peptides, amines or steroids. The endocrine system consists of various specialist cells in a variety of richly vascularised ductless glands that syn thesise and release hormones into the bloodstream. The neuroendocrine system involves neuroendocrine cells that receive nerve impulses to release neurohormones into the bloodstream. Neuroendocrine glands are found in almost every organ of the body . They are mainly found scattered in the gastrointestinal tract, pancreas (islet cells) and thyroid (C cells). For this reason they are known as the di ff use neuroendocrine system. A shared characteristic in the adrenal medulla, gut and pancreatic endocrine tissues are the amine precursor uptake and decarboxylation (APUD) cells, now known as neuroendo crine cells. For many years they were believed to have a com mon embryological derivation in the neural crest, from which cells migrated to tissues throughout the body . It is now believed that, along with neurones, they share a common neuroendo crine programming influence during their di ff er entiation (see Further reading). Finally , somatostatin receptors (SSTRs) are present on the cell surface of neuroendocrine cells, providing a unique and specific molecular target for imaging and therapy . Nuclear imaging physicians and specialists in radiopharma ceutical therapy are important additional members of the endocrine surgery multidisciplinary team. Dumitru Gerota , 1867–1939, Professor of Surgery , Bucharest, Romania. Throughout the chapter, the diagnosis and management of various conditions are considered. For each and every disease the principles of endocrine surgery are followed in a stepwise - manner: /uni25CF confirm the diagnosis with biochemical tests; /uni25CF render the patient safe (e.g. treat hypertension, hypoglycae - mia, hypokalaemia); /uni25CF consider whether localisation studies are necessary; - /uni25CF decide if surgery is indicated; /uni25CF if so, what operative approach is best?

To understand the immediate and long-term care after • surgery Multiple endocrine neoplasia (MEN syndromes) To understand the

genetics and various presentations of • patients with MEN

To be able to manage patients with MEN disorders and • familial medullary thyroid cancer To understand the principles of surgery and postoperative • management of patients with MEN

Learning objectives

Learning objectives

Adrenal gland To understand the investigation and diagnosis of disorders • of the adrenal gland To know of the principles and postoperative management • of adrenalectomy Pancreatic endocrine disorders and gastrointestinal neuro endocrine tumours (GI-NETs) To understand the investigation and diagnosis of • pancreatic endocrine tumours/GI-NETs To know the principles of management of pancreatic • endocrine tumours/GI-NETs, including surgery

Metastases

Metastases

Definition Adrenal metastases are not uncommon and often portend - disseminated incurable disease. Primary tumours that commonly spread to the adrenals include lung, renal, gastric, breast and colorectal cancers. The decision regarding surgical intervention must be multidis ciplinary and in conjunction with the patient, following careful diagnostic work-up to determine whether it is an isolated adre nal metastasis (seen most often with renal, lung and colorectal primaries) or a more widespread metastatic picture. Patients should therefore under go CT thorax, abdomen and pelvis and PET-CT to exclude disease at other sites. They should also be screened for catecholamine and cortisol excess to exclude a coincident hormonally active tumour. Treatment If disease is widespread, metastasectomy will not usually be appropriate and systemic or palliative treatment should be the norm. Adrenal metastasis diagnosed at presentation (synchro nous disease) should be removed if ipsilateral to a renal cell cancer (radical nephrectomy). In the case of other primary tumours, it should be observed with interval scanning at 3–6 months; if the lesion remains stable and isolated, resection should be considered. If adrenal metastasis arises more than 6 months after initial treatment (metachronous), PET-CT should be performed to exclude widespread disease; if the lesion is solitary , excision can be considered. Surgery Laparoscopic adrenalectomy is the preferred surgical option. Metastases often induce a significant desmoplastic reaction that can make excision more di ffi cult, particularly when lesions are >4 /uni00A0 cm. If there is evidence of local invasion, but the surgery is likely to improve survival, open surgery and bloc excision may be appropriate. Note that, in the setting of previous nephrectomy with adrenalectomy , excision of an Thomas Addison , 1795–1860, physician, Guy’s Hospital, London, UK, described the e ff ects of disease of the suprarenal capsules in 1852. Rupert Waterhouse , 1873–1958, physician, Royal United Hospital, Ba Carl Friderichsen , 1886–1979, Medical Superintendent, Sundby Hospital, Copenhagen, Denmark, gav steroid dependent. - -

TABLE 57.1 Causes and classi /f_i cation of adrenal insuf /f_i ciency. Cause of adrenal insuf /f_i ciency Pathophysiology Autoimmune adrenalitis (polyglandular Serum antibodies against the steroidogenic enzymes autoimmune syndromes) Infective tuberculous disease Caseating granulomatous destruction Bilateral adrenal infarction Severe bacterial sepsis in children, e.g. meningococcal septicaemia Bilateral adrenal haemorrhage Traumatic obstetric delivery Malignancy In /f_i ltration by secondary cancers Congenital adrenal hyperplasia (adrenogenital Genetic disorders of steroidogenesis syndrome) Pituitary destruction Infarction, trauma, haemorrhage or in /f_i ltration, e.g. craniopharyngioma Cessation of chronic glucocorticoid therapy Zona fasciculata and reticularis atrophy owing to long-term CRH suppression by exogenous corticosteroids Treatment of Cushing’s syndrome and Cushing’s CRH suppression following removal of ACTH-secreting or disease cortisol-secreting tumours Hypothalamic disorders Trauma, stroke, tumour in /f_i ltration, radiation, infection ACTH, adrenocorticotropic hormone; AI, adrenal insuf /f_i ciency; CRH, corticotropin-releasing hormone. a Waterhouse–Friderichsen syndrome.

PHYSIOLOGY

PHYSIOLOGY

The outer zona glomerulosa secretes the C21 steroid aldosterone. The zona fasciculata secretes (C21 steroid) cortisol and the inner zona reticularis secretes (C19 steroid) androgens. Aldosterone regulates sodium–potassium homeostasis; it promotes sodium retention and potassium excretion. The target organs of aldosterone are the kidneys, the sweat and salivar y glands and the intestinal mucosa. The most important regulators of aldosterone secretion are the renin–angiotensin system and serum potassium concentration. Renin, produced by the juxtaglomerular cells in the kidneys, acts on its substrate angiotensinogen to generate angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to the octapeptide angiotensin II, which is modified to angiotensin III. Both stimulate secretion of aldosterone from the adr enal cortex. A decrease in renal blood flow (haemorrhage, dehydration, salt depletion, orthostasis, renal artery stenosis) or hyponatraemia increases renin secretion, resulting in sodium retention, potassium excretion and an - increased plasma volume. Cortisol secretion by the cells of the zona fasciculata is regulated by adrenocorticotropic hormone (ACTH), which is produced by the anterior pituitary gland. The hypothalamus controls ACTH secretion by secreting corticotropin-releasing hormone (CRH). The serum cortisol level inhibits the release of CRH and ACTH via a closed-loop system (negative feed - back loop). Cortisol has numerous metabolic and immunological e ff ects. It increases gluconeogenesis and lipolysis, decreases - peripheral glucose utilisation, inhibits immunological response and, in time, reduces muscular mass. It a ff ects fat distribution, wound healing and bone mineralisation; it also alter s mood (causing euphoria or, rarely , depression) and brain cortical activity and alertness. Cells in the zona reticularis synthesise adrenal androgen dehydroepiandrosterone (DHEA) and its sulphate, DHEAS. Adrenal androgen accounts for about 20% of total male activity and is under the control of ACTH. Cells of the adrenal medulla synthesise mainly adrenaline (epinephrine; 80%) but also noradrenaline (norepinephrine; 20%) and dopamine. Unlike other adr energic neurones, those of the medulla express phenylethanolamine- N - methyltransferase (PNMT), which catalyses the conversion of noradrenaline to adrenaline. These catecholamines act as hormones as they are secreted directly into the circulation. Their e ff ects, which are mediated through α and β receptors on target organs, include - the cardiovascular system, resulting in an increase in blood pressure, heart rate and cardiac contractility; vasoconstriction of vessels in the splanchnic system and vasodilatation of vessels lysis in liver and muscles, all of which are necessary for the flight/fight response.

Treatment

Treatment

Medical Metyrapone or ketoconazole therapy reduces steroid synthesis and secretion by CYP11B1 inhibition and can be used to prepare patients with severe hypercortisolism preoperatively or as primary therapy if surgery is not possible. In patients who are critically ill with Cushing’s syndrome, intravenous etomidate infusion (even at non-hypnotic doses) can reduce serum cortisol levels to normal within 24 hours, providing a suitable window for surgery . This requires monitoring in an intensive care unit setting. Surgical ACTH-producing pituitary tumours are treated by trans - sphenoidal resection and/or radiotherapy . Resection of ectopic ACTH-secreting tumours will also correct hypercortisolism. Patients who have undergone failed pituitary surgery or those with an unresectable or unlocalised ectopic ACTH-secreting tumour may require bilateral adrenalectomy to control hormone excess. This will render them steroid dependent. Unilateral adenoma should be treated by minimally invasive adrenalectomy provided adrenocortical cancer is not suspected. In cases of bilateral ACTH-independent disease (Figure 57.6), the extent of adrenalectomy is contentious; bilateral adrenalectomy should be employed in severe Cushing’s and equally enlarged adrenals. In asymmetric disease, excision -

Figure 57.6 Bilateral asymmetrical hyperplasia of the adrenal glands (arrows) in a patient with Cushing’s syndrome.

In cases of subclinical Cushing’s syndrome and a unilateral adenoma, unilateral adrenalectomy is indicated if the tumour is >4 /uni00A0 cm or <4 /uni00A0 cm with features of the metabolic syndrome. Cushing’s syndrome predis poses patients to increased risk of venous thromboembolism, cardiac events, infection and poor wound healing. Patients should therefore receive chemical and mechanical thrombo prophylaxis as well as perioperative broad-spectrum antibiotics. Accompanying diabetes should also be adequately controlled. As unilateral or bilateral adrenalectomy in the setting of Cushing’s syndrome will result in steroid deficiency in the postoperative period, patients should r eceive intraoperative corticosteroids (50–100 /uni00A0 mg intravenous hydrocortisone) and close liaison with the endocrinology team is strongly advised to guide postoperative management. After unilateral adrenalectomy the contralateral gland will be suppressed and so all patients should be commenced on 15–25 /uni00A0 mg daily of hydrocortisone. In total, 15 /uni00A0 mg/h is requir ed parenterally for the first 12 hours followed by a daily dose of 100 /uni00A0 mg for 3 /uni00A0 days, which is gradually reduced thereafter. After unilateral adrenalectomy , the contralateral suppressed gland may need up to a year to recover adequate function. A synacthen test is used to confirm adequate adrenal function prior to stopping hydrocortisone supplementation. In 10% of patients with Cushing’s disease who undergo a bilateral adrenalectomy after failed pituitary surgery , the pituitary adenoma causes Nelson’s syndrome owing to continued ACTH secretion at high levels, resulting in hyperpigmentation due to uncontrolled secretion of pro-opiomelanocortin (POMC). POMC is cleaved to produce ACTH and melanocyte-stimulating hormone, excess of the latter resulting in hyperpigmentation.

Preoperative management. Postoperative management.