Cushing’s syndrome

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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.

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