Diagnosis

Cushing's syndrome (CS) results from chronic exposure to excess glucocorticoids (GC) produced by the adrenal cortex.

CAUSES: CS may be caused by excess ACTH production by a pituitary adenoma and less frequently by an extrapituitary tumor (ectopic ACTH syndrome). CS can also be ACTH-independent when it results from excess secretion of cortisol by adrenocortical tumors or by bilateral adrenal hyperplasia.

In the large population described in the ERCUSYN study, we found that 66% of patients had a pituitary adenoma, 27% had an adrenal tumor, 5% had an ectopic syndrome and 2% an adrenal hyperplasia.

CLINICAL PRESENTATION: The following clinical findings should arise the suspicion of CS: central obesity with supraclavicular fat accumulation, a cervical fat pad, thinned skin, purple striae, proximal muscle weakness, fatigue, high blood pressure, glucose intolerance, acne, hirsutism, menstrual irregularity and depression. In the ERCUSYN study we showed that weight gain, hypertension, skin alterations and myopathy were the most frequent symptoms at diagnosis in the entire series. The presence of skin alterations, menstrual irregularities and hirsutism more reliably distinguished pituitary dependent CS from adrenal CS. Diabetes mellitus and hirsutism were more prevalent in patients with the ectopic syndrome than in the other patients, suggesting that clinical presentation of CS may vary based on the etiology.

DIAGNOSIS: The diagnosis of CS should start with a careful case history and a thorough physical examination. Importantly, clinicians should rule out recent use of oral, inhaled, parenteral, or topical GC. In the presence of a clinical picture suggestive of CS, a first-line test should be chosen among the following: urine cortisol measurements/24 h (UFC) (at least two measurements), late night salivary cortisol (at least 2 measurements), or overnight 1-mg dexamethasone suppression test (DST). In those conditions characterized by physiologic hypercortisolism, including diabetes mellitus, depression, alcoholism, and morbid obesity, the 48-h, 2 mg/d low-dose DST could be more reliable than urine or salivary cortisol assessment. In the presence of any abnormal result, clinicians should exclude physiologic causes of hypercortisolism, repeat the abnormal test and perform further evaluation. Referral to an endocrinologist in a specialized centre is highly recommended in case of uncertain diagnosis and equivocal results on testing.

Treatment

PITUITARY-DEPENDENT CS: The treatment of choice for pituitary-dependent CS is surgical resection of the pituitary adenoma. Remission rates after transsphenoidal microsurgery of pituitary adenoma are in the range of 65-90% for microadenomas (<1 cm) and less than 65% for macroadenomas (≥1 cm), depending on the surgeon's expertise.

Postoperative hypocortisolaemia and the need for glucocorticoid replacement are positive predictors of long-term remission of pituitary-dependent CS but are not a guarantee of cure. Patients with cortisol levels less than 2 μg/dl, as assessed in the first postoperative week, may have a lower risk for recurrence than those with values above 5 μg/dl, but this point is still matter of debate. A subset of patients may experience a progressive decline of cortisol levels in the postoperative period, achieving a delayed remission. This suggests that expectant management for three months until cortisol levels reach a nadir may be advisable to spare some patients further, unnecessary treatment.

POST-SURGERY REPLACEMENT: In the presence of postsurgical hypocortisolaemia, GC replacement (hydrocortisone 12-15 mg/m^2 or an equivalent) must be started until the pituitary-adrenal axis recovers. Periodic assessment of the pituitary-adrenal function must be performed and replacement therapy can be withdrawn when morning cortisol levels or post-cosyntropin cortisol is greater than 18 μg/dl (500 nmol/L).

ECTOPIC CS: In patients with an ectopic source of ACTH, cure may be achieved if the tumor is benign and amenable to surgery. In patients with metastatic disease, palliative surgery may be an option.

ACTH-INDEPENDENT CS: Adrenalectomy is the treatment of choice for ACTH-independent CS. Laparoscopic adrenalectomy is now the favorite approach in many centres for its safety and cost-effectiveness. Patients undergoing a bilateral adrenalectomy need long-life replacement with GC and mineralcorticoids. After unilateral adrenalectomy, GC are necessary until full recovery of the pituitary-adrenal axis is achieved.

RADIOTHERAPY: Radiotherapy may be used as a second-line treatment of failed pituitary surgery. Fractionated external beam radiotherapy or stereotactic radiosurgery can control hypercortisolaemia in approximately half of patients within 3-5 years.

MEDICAL THERAPY: Medical therapy with steroidogenesis inhibitors (ketoconazole, metyrapone) may be used prior to surgery to control hypercortisolaemia and its deleterious effects and, possibly, to reduce postoperative complications. Medical therapy should be used in patients who have undergone radiotherapy, while waiting for the treatment to be effective. Medical therapy should also be used in patients who have been unsuccessfully treated with surgery and/or radiotherapy, prior to bilateral adrenalectomy.

NEW TREATMENTS: Efficacy and safety of tumor-directed medical therapy (such as cabergoline and SOM230) in patients with ACTH-secreting pituitary adenomas are currently under investigation.