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# Florid Cushing's Syndrome

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## CLINICAL RECOGNITION

Cushing's syndrome (CS) results from long-standing exposure to supraphysiologic concentrations of circulating glucocorticoids. Untreated CS is associated with a high morbidity and increased mortality rates mainly because of its metabolic abnormalities and the risk of infection. When the presentation is florid, the diagnosis is usually straightforward (Tables 1 and 2). However, diagnosis might be complicated by the non-specificity of some of the clinical symptoms; notably, the signs that most reliably distinguish CS from obesity are those of protein wasting – the presence of thin skin, easy bruising, and proximal muscle weakness.

### Table 1 Signs, Symptoms of Cushing's Syndrome

| Signs | Symptoms |
|---|---|
| Buffalo hump, moon face; flushing/red face<br>Weight gain/ central obesity<br>Easy bruising/ecchymosis<br>Proximal myopathy/wasting/muscular atrophy<br>Purplish skin striae<br>Skin pigmentation<br>Thin skin/ skin disorders<br>Edema;<br>Fundal abnormalities<br>Hair thin, dry<br>Loss of weight<br>Poor growth/short stature;<br>Facial hirsutism (±frontal balding)<br>Fine non-pigmented vellus hair<br>Acne | Fatigue, lethargy, poor exercise ability<br>Headaches/migraines<br>Joint aches<br>Sweating<br>Visual disturbances<br>Thirst/polydipsia<br>Loss of libido<br>Poor memory<br>Poor concentration<br>Slowed responses |

| | |
|---|---|
| Virilization<br>Galactorrhea | |

**Table 2 Disorders Associated with Cushing's Cyndrome**

| |
|---|
| Hypertension/ CVD/ prolonged QTc dispersion/ LVH |
| Hyperhomocysteinemia/ increased thrombotic tendency |
| Diabetes |
| Obesity/ increased visceral fat/ hepatic steatosis |
| Infection |
| Depression/ emotional lability/ anxiety/ sleep disorders/ lethargy/ psychosis/ psychiatric disorders |
| Hypogonadotrophic hypogonadism |
| Osteoporosis/ vertebral fractures |
| Cognitive/memory impairment |
| Renal stones |
| Thyroid disorders |
| Growth retardation |
| Menstrual disorders/ PCO |

## PATHOPHYSIOLOGY

See http://www.endotext.org/neuroendo/neuroendo7/neuroendoframe7.htm

## DIAGNOSIS and DIFFERENTIAL DIAGNOSIS

The most common cause of CS is the use of supraphysiological amounts of exogenous glucocorticoids. (Table 3) Typically this is of moderate severity, and not an emergency. A detailed drug history is essential for diagnosis.

**Table 3 Etiology of Cushing's Syndrome**

| **Exogenous causes** |
|---|
| Exogenous glucocorticoid administration<br>Iatrogenic<br>Drug--drug interactions (via hepatic enzyme CYP3A4 and P-glycoprotein (PGP) export pump)<br>Factitious |
| Exogenous ACTH administration<br>Iatrogenic |
| **Endogenous causes** |
| ACTH-dependent (80-85%)<br>Cushing's disease (80%)<br>Ectopic ACTH syndrome (20%)<br>Ectopic CRH syndrome (<1%) |
| ACTH-independent (20%)<br>Adrenal adenoma (60%)<br>Adrenal carcinoma (40%)<br>ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH)±secondary to abnormal hormone receptor expression/function or armadillo repeat-containing-5 (ARMC5) gene mutations (<1%)<br>Sporadic or associated with Carney complex primary pigmented nodular adrenal disease (PPNAD) or micronodular adrenal disease(<1%)<br>Bilateral nodular adrenal disease in McCune-Albright syndrome (<1%)<br>Constitutive activation ACTH receptor by missense mutation (<1%) |

Endogenous CS is more common in women. Corticotrophin (ACTH)-dependent CS is caused mainly by a pituitary corticotroph adenoma (Cushing's disease, CD) secreting ACTH, or by an extra-pituitary tumor (ectopic ACTH syndrome, EAS, (Table 4). ACTH-independent CS is caused by unilateral adrenocortical tumors or by bilateral adrenal hyperplasia or dysplasia.

In ACTH-dependent CS, elevated ACTH secretion results in excess adrenal gland cortisol secretion. The normal cortisol feedback mechanism of the hypothalamic-pituitary-adrenal (HPA) axis is distorted, with loss of the circadian rhythm, excess cortisol production, and loss of normal suppression to the exogenous administration of glucocorticoids. EAS can have a rapid onset with severe features, although in some patients a paraneoplastic wasting syndrome can mask the hypercortisolism. The metabolic abnormalities such as hyperglycemia and hypokalemia tend to be more florid in EAS.

**Table 4 Tumors More Frequently Associated with Ectopic ACTH Syndrome**

| **Tumors** | **Percentage reported (%)** |
|---|---|
| Small cell lung carcinoma | 3.3-50 |
| Bronchial carcinoids | 5-40 |
| Islet cell tumors/ pancreatic carcinoids | 7.5-25 |

| | |
|---|---|
| Thymic carcinoids | 5-42 |
| Pheochromocytoma | 2.5-25 |
| Medullary thyroid carcinoma | 2-8 |
| Gastrinoma | 5 |
| Tumour not identified | 12-37.5 |

In ACTH-independent CS, the most common pathology is an adrenal adrenocortical adenoma (AAA) or carcinoma (AAC) (Table 3). Adrenal adenomas occur most often around 35 years of age and are more common in women with an incidence of approximately 0.6 per million per year. The incidence of ACC is approximately 0.2 per million per year. Different frequencies have been observed in childhood (Table 5).

**Table 5 Cushing's Syndrome Presence In Children**

| | Age group | Mean age (yr) |
|---|---|---|
| McCune Albright syndrome | infants | 1.2 |
| Adrenal adrenocortical carcinoma | young children | 4.5 |
| Ectopic ACTH syndrome (rare) | older children | 10.1 |
| Primary pigmented nodular adrenal disease | adolescents | 13.0 |
| Cushing's disease | adolescents | 14.1 |

## DIAGNOSTIC TESTS NEEDED AND SUGGESTED

Diagnostic assessment is usually prompted by clinical suspicion in cases of florid CS seen as medical emergencies. In the investigation of CS, the initial biochemical tests should ideally have maximal sensitivity rather than specificity in order to identify individuals with the mild forms of this rare disease; later, more specific tests are used to exclude false positives (Table 6). Hypercortisolemia must be established before any attempt at the differential diagnosis. A combination of the following tests is initially used: 24-h urinary free cortisol (UFC), ideally measured by liquid chromatography tandem-mass spectrometry to improve accuracy, low-dose dexamethasone suppression test (LDDST) or overnight dexamethasone test (ODST), and assessment of midnight serum cortisol (MSeC) or late-night salivary cortisol (LNSaC) (Tables 6 and 7). ***However, it should be emphasized that in cases presenting with severe disease, a massively elevated serum cortisol at any time, or a urinary cortisol more than 4x the upper limit of normal, is sufficient to confirm the diagnosis. No other tests may be required for the diagnosis.***

**Table 6 Tests Used For The Establishment Of Hypercortisolemia**

| | | Normal |
|---|---|---|

| | | |
|---|---|---|
| 24-hr UFC | free cortisol/ creatinine measurement | 3 normal collections |
| ODST | 1mg dexamethasone midnight | <50nmol/L(<1.8μg/dL) 9:00 next morning |
| LDDST | 0.5mg dexamethasone/6hr for 48hrs (09.00 day0; post-48hrs) | <50nmol/L(<1.8μg/dL) |
| MSeC/ LNSaC | Midnight/23:00hr | Saliva: Local<br>range; serum: asleep<50nmol/L, awake: 207 nmol/l (7 μg/dL) |
| LDDST: Low-dose dexamethasone suppression test;<br>LNSaC: late-night salivary cortisol<br>MSeC: midnight serum cortisol;<br>ODST: overnight dexamethasone suppression test;<br>UFC: urinary free cortisol | | |

The second step in the diagnostic cascade of CS is to establish the cause by measuring plasma ACTH. Values in the 'grey zone' are the most challenging since patients with both CD and adrenal pathologies might have intermediate values. ***However, a plasma ACTH above 20 ng/L will immediately establish ACTH-dependence, while levels below 10 ng/L will lead to the search for adrenal pathology. If ACTH is present, then the patient either has Cushing's disease or an ectopic source.*** A positive ACTH and/or cortisol response to the CRH test will suggest Cushing's disease, a poor response to either the LDDST or the high-dose test likewise, but bilateral inferior petrosal sinus sampling (BIPSS) is generally advised in all cases except when (1) there is an obvious macroadenoma on MRI of the pituitary, or (2) the patient is too ill and requires immediate medical therapy. Data on the utility of these tests are given in Table 7.

**Table 7 Test Used For The Differential Diagnosis Of Hypercortisolemia**

| | | |
|---|---|---|
| HDDST | 2mg dexamethasone/6hr for 48hrs (09.00 day0; post-48hrs) | cortisol suppression >50%: CD; sensitivity:60-100%; specificity:65-100% |
| hCRH/oCRH test | iv-bolus 1μg/kg or 100 μg | o-CRH: ACTH > 35%/ or cortisol > 20% specific for CD; h-CRH: ACTH > 105%/ or cortisol >14; sensitivity:94%; |

| | | |
|---|---|---|
| BIPPS | ACTH pituitary-to-periphery gradient | Basal central-to-peripheral ratio > 2, or post-CRH>3: CD; sensitivity/specificity: 94% |
| ACTH levels (±potassium, bicarbonate) | | < 1.1pmol/L (5pg/mL) ACTH-independent CS; > 3.3pmol/L (15pg/mL) ACTH-dependent pathologies; in-between further investigation |
| BIPPS: Bilateral inferior petrosal sinus sampling;<br>CRH: corticotrophin releasing hormone;<br>CS: Cushing's syndrome;<br>h-CRH: recombinant human;<br>CRH HDDST: High-dose dexamethasone suppression test;<br>iv: intravenous; o-CRH: ovine-sequence CRH | | |

***If ACTH is very low or undetectable, then the next step is imaging of the adrenals.*** (Table 8). High-resolution computed tomography (CT) scanning of the adrenal glands gives the best resolution of adrenal anatomy and it is accurate for masses >1cm allowing evaluation of the contralateral gland. A mass >5 cm in diameter is considered to be malignant until proven otherwise.

**Table 8 Adrenal Gland Imaging In Different Types Of Cushing's Syndrome**

| Disease | Adrenal gland morphology |
|---|---|
| Adrenal tumours | typically unilateral mass + atrophic contralateral gland |
| PPNAD | normal or slightly lumpy (multiple small nodules); not enlarged |
| AIMAH | bilaterally huge (>5cm) with nodular pattern |
| ACTH-dependent forms of CS | enlarged (70%) |
| Cushing's disease | Enlarged ± nodules; adrenal hyperplasia not always symmetrical ± adrenal autonomy |
| EAS | virtually always homogeneously enlarged |

| | |
|---|---|
| Exogenous administrationof glucocorticoids | adrenal atrophy and very small glands. |
| AIMAH: • ACTH-independent bilateral macronodular adrenal hyperplasia; EAS: ectopic ACTH syndrome; PPNAD: primary pigmented nodular adrenal disease | |

Go to:

## THERAPY

The goals of treatment are the normalization of cortisol levels with a reversal of clinical symptoms. However, it is important in the short-term to manage the metabolic problems associated with florid CS. Diabetes needs to be controlled in the standard manner, often requiring **insulin**, while the blood pressure will also require urgent attention. **Hypokalemia** is a problem in almost all patients with EAS and some 10% of patients with other etiologies. **Spironolactone** at a dose of 50 or 100mg is usually effective, but **triamterene** is sometimes a good alternative. These patients also have a high pro-thrombotic tendency, and we would usually use **sc heparin** at prophylactic doses as opposed to severe cases where low molecular weight heparins should be used at therapeutic doses. Where the mental changes are severe and causing problems in management, **haloperidol** may be necessary to calm the patient, although there is also some experience with **olanzapine**.

These patients are at high risk of sepsis, often with minimal clinical signs, and any such infection must be vigorously treated. This includes bacterial, fungal and viral causes, as is seen in other immunosuppressed patients.

In terms of specific treatment of the hypercortisolemia (Table 9), where available **metyrapone** is rapid in onset and highly effective, but doses up to 1g qid may be required. Osilodrostat, displaying a similar profile but with higher potency and a better adverse effect profile, seems a promising currently experimental drug. **Ketoconazole** can be used additionally or in place of metyrapone, although its onset of action is slower, occurring over several days: up to 400mg tid may be used. As the dose is titrated upwards close monitoring of liver function tests is important. Levoketoconazole may have a better safety profile particularly regarding hepatotoxicity and is currently under trial. When neither drug alone or in combination is effective or tolerated, then intravenous **etomidate** at sub-anesthetic doses may be very useful: it acts within hours and is almost always very effective but should be administered in an intensive care unit. Finally, if all else fails, **mifepristone** 400-800mg daily can reduce the symptoms and signs of CS but there two caveats; serum cortisol cannot be used as marker of efficacy and the patient can become Addisonian unless care is taken, and severe hypokalemia may be induced (this is treatable with spironolactone).

In patients with severe infection, the serum cortisol should be lowered to a level compatible with that seen in other patients with life-threatening infection, which we

take as 600-1000 nmol/L. Some would prophylactically treat for the possibility of pneumocytis carinii pnemonia.

In the long-term, surgical removal of the tumor of ACTH-dependent or ACTH-independent origin is the first-line therapeutic approach. Anti-glucocorticoid medical treatment is usually required before surgery to reverse the metabolic consequences and poor healing or in patients who cannot undergo surgical procedures because of co-morbidities, or who are unwilling to receive other types of treatment.

**Table 9 Medical Treatment: Adrenal Secretion Inhibitors Or Adrenolytic Drugs**

| Drugs | Drawbacks | Blockage |
|---|---|---|
| Metyrapone | Escape phenomenon; hypertension, hypokalemia, edema; women: hirsutism | 11ß-hydroxylase |
| Osilodrostat | Possible escape phenomenon, weight gain, edema, hypernatremia, gastrointestinal effects, fatigue, headache, hypokalemia, | 11ß-hydroxylase and aldosterone synthase |
| Ketoconazole | Escape phenomenon; men: gynecomastia, hypogonadism; mild liver enzyme elevation; rarely: liver failure | cytochromeP450 enzymes (17,20-lyase; cholesterol side-chain cleavage,16a-/ 17a-/ 18-/ 11ß-hydroxylase |
| Levoketoconazole | better safety and efficacy compared to ketoconazole | mainly 21-hydroxylase, 17α-hydroxylase, 11β-hydroxylase |
| Etomidate | Sedation | 11ß-hydroxylase; 17ß-hydroxylase 17,20-lyase; cholesterol side chain cleavage |
| Fluconazole | Not well studied; possibly better tolerated compared to ketoconazole | As ketoconazole |
| Mitotane | Slow onset of action; digestive symptoms; neurotoxicity; hypercholesterolemia | Cholesterol side-chain cleavage 11ß- and 18-hydroxylase 3ß-hydroxysteroid dehydrogenase |
| Compounds targeting glucocorticoid function: Glucocorticoid antagonists | | |

| | | |
|---|---|---|
| mifepristone | No follow-up marker | Competitive binding to the glucocorticoid, androgen and progestin receptors |

In patients with CD trans-sphenoidal surgery (TSS) offers the potential to leave the remaining pituitary function intact. Initial remission rate is 60-80% but with a recurrence rate of up to 20% after prolonged follow-up. Macroadenoma remission rates are lower. Reoperation is possible. Hypocortisolemia in the immediate postoperative period needs glucocorticoid replacement treatment until HPA axis recovery. Postoperative concentration of cortisol <50nmol/L defines cure but is not predictive of no recurrence. After surgery failure, conventional **fractionated external beam radiotherapy** achieves control of hypercortisolemia in approximately 50–60% of patients within 3-5 years but with long-term hypopituitarism, and delayed effectiveness; this treatment seems more effective in children. Stereotactic radiosurgery has also been reported to be effective with probably the same time of onset of control, but as the beam is more focused there may be less hypopituitarism; the tumor needs to be well clear of the optic chiasm.

Resection of the causative tumor is the optimum treatment for EAS. If this is not feasible because of metastatic or occult disease an individualized approach has to be used.

In any cause of ACTH-dependent CS, **bilateral adrenalectomy** induces a rapid resolution of the clinical features after first-line treatment failure or when drugs are not effective or tolerated or when the rapid control of hypercortisolemia is crucial; however, patients will need lifelong treatment with glucocorticoids and mineralocorticoids besides the careful education and the meticulous evaluation of patients.

Adrenal gland removal laparoscopically is the treatment of choice for unilateral adrenal adenomas. Prognosis after removal of an adenoma is good, as opposed to ACC which is poor. Those latter tumors are not usually radiosensitive or chemosensitive and the most important predictor of favorable outcome in this disease is complete resection.

In AIMAH, cortisol secretion can be controlled in some cases by blocking the corresponding aberrantly expressed receptor (propranolol for aberrant β-adrenergic receptor expression; somatostatin analogues in gastric inhibitory peptide responsive AIMAH or leuprolide in luteinizing hormone dependent CS). However, most patients need bilateral adrenalectomy.

## FOLLOW-UP

Once the CS has been adequately treated, then long-term follow-up is mandated for all patients.

## GUIDELINES

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