Cushing's syndrome results from lengthy and inappropriate exposure to excessive glucocorticoids. Untreated, it has significant morbidity and mortality.

The most common cause of Cushing's syndrome is use of supraphysiological amounts of exogenous glucocorticoids, including topical or inhaled corticosteroids (iatrogenic Cushing's syndrome). Thus, adequate knowledge of an individual's medication history is essential for diagnosis.

Clinical features of Cushing's syndrome: obesity, purple striae, muscle atrophy, osteoporosis, and kidney stones more frequent in men. Gonadal dysfunction is common in both sexes. More than 70% of patients with Cushing's syndrome can present with psychiatric symptoms ranging from anxiety to frank psychosis if present, depression is often agitated in nature. Impairment in short-term memory and cognition is common. Effects of cortisol excess are associated with a reduction in apparent brain volume that slowly reverses after correction of hypercortisolaemia.

Cushing's disease and adrenal pathologies might have intermediate values.

(i) Medical therapies to lower cortisol
- Metyrapone, ketoconazole, and mitotane can all be used to lower cortisol by directly inhibiting synthesis and secretion in the adrenal gland.
- Metyrapone and ketoconazole are enzyme inhibitors and have rapid onset of action, but frequency control of hypercortisolism is lost with corticotropin oversecretion in Cushing's disease (known as escape).
- These drugs are not usually effective as the sole long-term treatment of the disorder, and are usually either in preparation for surgery or as adjunctive treatment after surgery, pituitary radiotherapy, or both procedures.
- For acute control of severe hypercortisolism when the oral route is not available, the short-acting anesthetic agent etomidate can be very useful, including in children.
- Prognosis after removal of an adenoma is good, although, by contrast, the outlook is almost uniformly poor in patients with adrenocortical carcinomas.

(ii) Pituitary surgery
- Several series, including many within the past 5 years, have shown the results and long-term follow-up of transsphenoidal surgery for Cushing's disease. Transsphenoidal surgery offers the potential for a selective microadenectomy of the causative corticotrope adenoma leaving the remaining pituitary function intact.

(iii) Adrenal surgery
- Laparoscopic surgery is now the treatment of choice for unilateral adrenal adenomas. Prognosis after removal of an adenoma is good, although, by contrast, the outlook is almost uniformly poor in patients with adrenocortical carcinomas.

(iv) Pituitary radiotherapy
- Persisting hypercortisolism after trans-sphenoidal surgery can be treated with pituitary radiotherapy. Conventional fractionated radiotherapy is a very effective means of treatment but is associated with long-term hypopituitarism, and can be very delayed in effectiveness, although it tends to be more rapidly curative in children. Use of stereotactic radiosurgery has also been reported.

1. Urinary free cortisol - Measurement of urinary cortisol is a direct assessment of circulating free (biologically active) cortisol. Excess circulating cortisol saturates the binding proteins and is excreted in urine as free cortisol, accounting for its usefulness as a marker of hypercortisolism.
   - Values four-fold greater than the upper limit of normal are rare except in Cushing's syndrome. A single measurement has low sensitivity for patients with intermittent hypercortisolism.

2. Low-dose dexamethasone-suppression tests - Two tests are in widespread use: the overnight and the 48-h dexamethasone-suppression tests. In the overnight test, 1 mg of dexamethasone is given at 2300 h and the concentration of cortisol in serum measured the next day at 0800-0900 h. In the 48-h test, dexamethasone is given at the dose of 0.5 mg every 6 h for 2 days (at 0600 h, 1200 h, 1800 h, and 0000 h) with measurements of cortisol in serum at 0900 h at the start and end of the test.
   - To exclude Cushing's syndrome, the concentration of cortisol in serum should be less than 50 nmol/L after either test.
   - The 48-h test, although more cumbersome than the overnight test, is more specific.
   - In both tests, caution needs to be exercised if there is potential malabsorption of dexamethasone or if patients are on drugs that increase hepatic clearance of dexamethasone, such as carbamazepine, phenytoin, phenobarbital, or rifampicin.

3. Midnight plasma cortisol
- Normal circadian rhythm of cortisol secretion is lost in patients with Cushing's syndrome. A single nighttime plasma cortisol concentration of less than 5 nmol/L effectively excludes Cushing's syndrome at the time of the test. Concentrations of more than 50 nmol/L are noted in individuals with Cushing's syndrome, even those who suppress serum cortisol on low-dose dexamethasone testing, but this cutoff lacks specificity because patients with acute illness also have values above this concentration.

Figure 2: Diagnosis of cause of Cushing's syndrome

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence</th>
<th>Female/male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's disease</td>
<td>70%</td>
<td>55.4%</td>
</tr>
<tr>
<td>Adrenal adenoma</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>Adrenal carcinomas</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Macronodular hyperplasia</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Primary pigmented nodular adrenocortical disease</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Multiple adenomas</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Related information:
- Cushing's syndrome is more common in females, especially if they are using oral contraceptives.
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Additional notes:
- Signs that most reliably distinguish Cushing's syndrome from obesity are those of protein wasting-presence of thin skin in the young, easy bruising, and proximal weakness.
- Data shows the difference in presentation between women and men, with purple striae, muscle atrophy, osteoporosis, and kidney stones more frequent in men. Gonadal dysfunction is common in both sexes.
- More than 70% of patients with Cushing's syndrome can present with psychiatric symptoms ranging from anxiety to frank psychosis if present, depression is often agitated in nature.
- Impairment in short-term memory and cognition is common and can persist for at least a year after treatment. These effects are associated with a reduction in apparent brain volume that slowly reverses after correction of hypercortisolism.
- Cortisol excess predisposes to hypertension and glucose intolerance.