Cushing’s Syndrome and Hypercortisolism—Diagnosis and Treatment

Cortisol preparations are frequently used in modern medicine. Several patients depend on their frequent use, suggesting that hypercortisolism is a relatively common disease. Therefore, it is a common topic tested in examinations. Read all the important facts underlying hypercortisolism and Cushing's syndrome in order to correctly diagnose the disease and initiate the key treatment steps.

Definition and Etiology of Hypercortisolism

Exogenous hypercortisolism induced by long-term treatment with glucocorticosteroids can be distinguished from an endogenous increase in the synthesis and secretion of cortisol or ACTH.

In all cases, hypercortisolism is accompanied by Cushing’s syndrome. Exogenous hypercortisolism is the most common cause of Cushing’s syndrome. Endogenous Cushing’s syndrome can be distinguished into ACTH-dependent (secondary hypercortisolism) and ACTH-independent (primary hypercortisolism) types:
The presence of ACTH-producing adenoma in the anterior pituitary, or a primary hypothalamic hyperfunction, indicates central Cushing’s syndrome, which is also known as Morbus Cushing. ACTH-producing adenomas constitute the biggest group of endogenous Cushing’s syndromes.

- ACTH can be increased ectopically (paraneoplastic) due to small-cell lung carcinoma and carcinoid tumors.
- Reversible increase in ACTH may also occur due to alcohol consumption.
- ACTH-independent Cushing’s syndrome may result in cortisol-producing adenoma or carcinoma of the adrenal cortex (adrenal Cushing’s syndrome).

Epidemiology of Cushing’s Syndrome

While the exogenous (iatrogenic) Cushing’s syndrome is very common, its endogenous counterpart affects only 2–3 individuals in a population of 1 million. Almost 3/4 of such patients manifest central Cushing’s syndrome, up to 10% are due to ectopic (paraneoplastic) ACTH secretion, and about 15% manifest the ACTH-independent form, the adrenal Cushing’s syndrome.

Causes of Cushing’s syndrome:

- **Iatrogenic:** mostly due to exogenous administration of glucocorticoids
- **ACTH-independent:** adrenal hypersecretion of cortisol (adrenal adenoma, carcinoma, or hyperplasia)
- **ACTH-dependent:**
  - Pituitary hypersecretion of ACTH: Cushing’s disease
  - Ectopic hypersecretion of ACTH: Bronchial carcinoids; small cell carcinoma of the lung

Symptoms of Hypercortisolism

The clinical presentation by the affected patients is attributed to the myriad effects of cortisol, and the effects on fat metabolism are very distressing. Truncal obesity with a characteristic ‘bull’s neck’ and ‘moon face’ is attributed to fat redistribution. The skin shows defective tissue repair with a predisposition to hemorrhages (ecchymosis,
hematoma), acne, striae rubrae, atrophy, ulcers, and furuncles.

**Protein metabolism** with [osteoporosis](#) (and an increased risk for fractures or bone necrosis), myopathy with peripheral muscular atrophy, and adynamia are the other manifestations. Diabetic metabolic state may develop. In addition, **arterial hypertonia** may occur or be exacerbated. Androgen levels may also be increased in ACTH-dependent forms manifesting as **virilization with hirsutism and cycle disorders in women**.

**Hypokalemia**, which arises only in a few cases connected with hypercortisolism, may indicate a **tumor in the adrenal cortex** or ectopic ACTH synthesis.

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**Diagnostic Investigation of Hypercortisolism**

The diagnosis is based on clinical symptoms or the patient’s medication history.

First, a **low-dose dexamethasone inhibition test** is carried out to evaluate hypercortisolism using 2 mg dexamethasone obtained late in the evening. Physiologic suppression of endogenous cortisol production should occur the next morning. Hypercortisolism, whose etiology has yet to be determined, is evident in the absence of the following results the next morning.

**Plasma ACTH**: increased with central or ectopic Cushing’s syndrome; decreased with adrenal Cushing’s syndrome

**Corticotropin-releasing-hormone (CRH)**: ACTH concentration is measured before and after CRH dose. Hypothalamic hyperfunction and pituitary adenoma (= Cushing’s syndrome) show an ACTH increase after CRH dose. The increase fails to occur in patients with ectopic and paraneoplastic Cushing’s syndrome.

**High-dose dexamethasone inhibition**: Patients are administered 8 mg of dexamethasone for 2 days at midnight, which suppresses cortisol in the case of central Cushing’s syndrome. The cortisol suppression fails to occur in patients with tumors of the adrenal cortex or ectopic cortisol production.

In addition, **diagnostic imaging of sella turcica or adrenal cortex with CT or MRI** can be used to establish hypercortisolism. Paraneoplastic ACTH increases may be accompanied occasionally by an increase in the metabolite lipotropin.
Differential Diagnosis of Hypercortisolism

Compared with the various etiological factors contributing to 'real' hypercortisolism, the levels of cortisol as a stress hormone might be increased in different psychiatric disorders (e.g., depression). Cushing's syndrome is not always associated with every random tumor of the adrenal cortex. Hormone-unrelated forms are referred to as incidentalomas. Obesity is another differential diagnosis.

Treatment of Hypercortisolism

The treatment of hypercortisolism is based on etiology. Hormonally active tumors of the adrenal cortex can be excised with minimal invasion via laparoscopic adrenalectomy. The contralateral adrenal gland generates the hormones. However, a temporary substitution with glucocorticoids may be needed. Central Cushing's syndrome can also be managed surgically. A radiotherapy is an alternate option.

Note: In this case, post-surgical glucocorticoid supplementation is necessary for life, to avoid the risk of Addison's disease. The dose should also always be adjusted or increased depending on the clinical condition (for example, during profound stress situations, fever and other strains).

Inoperable tumors of the adrenal cortex or paraneoplastic or ectopic Cushing's syndrome, which is a phenomenon of ACTH Cushing's syndrome, can be treated symptomatically by blocking the cortisol production. Several preparations are currently available including ketoconazole, octreotide, metyrapone, and aminoglutethimide.

References

