Cortisol preparations are frequently used drugs in modern-day medicine. A lot of people are durably dependent on their frequent use. Thus, hypercortisolism is a relatively common disease and, therefore, a quite common exam topic. Read all the important facts on hypercortisolism and Cushing’s syndrome in order to correctly diagnose this disease and initiate the main steps of the treatment.

Definition and Etiology of Hypercortisolism

The etiology differentiates between an **exogenous hypercortisolism**, due to long-term treatment with glucocorticosteroids, and an **endogenous increased production and secretion of cortisol or ACTH**.

In all cases, hypercortisolism is followed by **consecutive Cushing’s syndrome**. The exogenous hypercortisolism is the most common cause of this condition. When it comes to the endogenous Cushing’s syndrome, it is necessary to differentiate between the
ACTH-dependent version (secondary hypercortisolism) and the ACTH-independent version (primary hypercortisolism):

- An ACTH-producing adenoma in the anterior pituitary, or a primary hypothalamic hyperfunction, indicates central Cushing's syndrome, which is also called Morbus cushing. This forms the biggest group of endogenous Cushing's syndromes.
- ACTH can be increased ectopically (paraneoplastic), too, due to small-cell lung carcinoma and carcinoid tumors.
- A reversible increasing of ACTH is also possible due to consumption of alcohol.
- The ACTH-independent Cushing's syndrome may underlie, for example, a 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 of 1 million inhabitants. 75% of those belong to the central Cushing’s syndrome, up to 10% are due to ectopic (paraneoplastic) ACTH-secretion, and about 15% correspond to the ACTH-independent form, the adrenal Cushing's syndrome.

Causes of Cushing’s syndrome:

**Iatrogenic:** Exogenous administration of glucocorticoids; most common

**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 in the affected patients stems from the various effects of cortisol. The effects on fat metabolism are certainly very disturbing. Truncal obesity with bull’s neck and moon face arises due to fat redistribution. The skin shows bad tissue repair with a predisposition for hemorrhages (ecchymosis, hematoma), acne, striae rubrae, atrophy, ulcers, and furuncles.

A catabolic protein metabolism with osteoporosis (and an increased risk for fractures or bone necrosis), myopathy with peripheral muscular atrophy and adynamia exist. Furthermore, a diabetic metabolic state is provoked. Arterial hypertonia may also arise or be worsened. Androgen levels may also be increased if it is an ACTH-dependent form: women experience virilization with hirsutism and cycle disorders.

A hypokalemia, which arises only in few cases connected with hypercortisolism, may be an indicator for a tumor of the adrenal cortex or for the ectopic ACTH-production.

Diagnostic Investigation of Hypercortisolism

The clinical symptoms or the patient’s medication history lead to the suspected diagnosis.

First, the low-dose dexamethasone inhibition test is carried out to further test the existence of hypercortisolism: 2 mg dexamethasone is taken late in the evening. Thus, it should actually come to a physiologic suppression of the endogenous cortisol production in the next morning. A hypercortisolism, whose etiology has to be explored, is evident if these are not true the next morning:

ACTH-determining in the plasma: increased with central or ectopic Cushing’s syndrome; decreased with adrenal Cushing’s syndrome.

Corticotropin-Releasing-Hormone (CRH) test: the ACTH-concentration is measured before and after CRH-dose. Hypothalamic hyperfunctions and pituitary adenoma (=Cushing’s syndrome) experience an ACTH-increase after CRH-dose. This increase fails to appear with ectopic, paraneoplastic Cushing’s syndrome.

High-dose dexamethasone inhibition test: 8mg dexamethasone are given for 2 days at midnight. This leads to cortisol suppression with a central Cushing’s syndrome. It
fails to appear with a tumor of the adrenal cortex or ectopic cortisol production.

In addition to that, the diagnostic imaging of the sella turcica or the adrenal cortex with CT or MRI might be useful. Paraneoplastic ACTH-increases are sometimes accompanied by an increase of the metabolite lipotropin.

**Differential Diagnosis of Hypercortisolism**

One has to keep in mind, next to the various reasons of a “real” hypercortisolism, that cortisol as a stress hormone might be increased due to different psychiatric diseases (e.g., depression). Not every randomly found tumor of the adrenal cortex has to carry a Cushing’s syndrome with it. Hormone-unproductive forms are referred to as incidentaloma. Obesity is another differential diagnosis.

**Therapy of Hypercortisolism**

The treatment conforms to the reason behind the hypercortisolism. Hormonally active tumors of the adrenal cortex can be removed with minimal invasion by laparoscopic adrenalectomy. The opposite site takes over the hormone production, but a substitution with glucocorticoids might be necessary for a certain period of time. Central Cushing’s syndrome can also be taken care of surgically. Radiotherapy is an alternate option.

Note: In this case, a post-surgical substitution with glucocorticoids is necessary for life (risk of Addison crisis)! The dose should also always be adapted and increased in certain situations (for example, during profound stress situations, fever and other strains).

Inoperable tumors of the adrenal cortex or paraneoplastic ACTH-syndromes can be treated symptomatically by blocking the cortisol production. Several preparations are available for this purpose (ketoconazole, octreotide, metyrapone, aminogluthethimide).

**Popular Exam Questions on Hypercortisolism and Cushing’s Syndrome**

The correct answers are below the references.

1. **Mrs. H. is being remitted from her primary physician to your internal division with the suspicion about a Cushing’s syndrome. Which of the following symptoms belongs least to the typical appearance of a Cushing’s syndrome?**
   - A. Striae rubrae distensae
   - B. Moon face
   - C. Night sweat
   - D. Skin atrophy and wound infection
   - E. Muscular atrophy of the limbs

2. **Cushing’s syndrome is, in most cases, related to:**
3. **Which findings are most likely due to an ectopic Cushing’s syndrome?**

A. Lowered ACTH-level in the plasma, no ACTH-increase after CRH-dose.
B. Lowered ACTH-level in the plasma, ACTH-increase after CRH-dose.
C. Increased ACTH-level in the plasma, cortisol-increase after CRH-dose.
D. Increased ACTH-level in the plasma, no cortisol-increase after CRH-dose.
E. No cortisol-increase after CRH-dose, but ACTH-increase after CRH-dose.

**References**


**Correct answers:** 1C, 2B, 3D

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