Cushing's Syndrome Hypercortisolism

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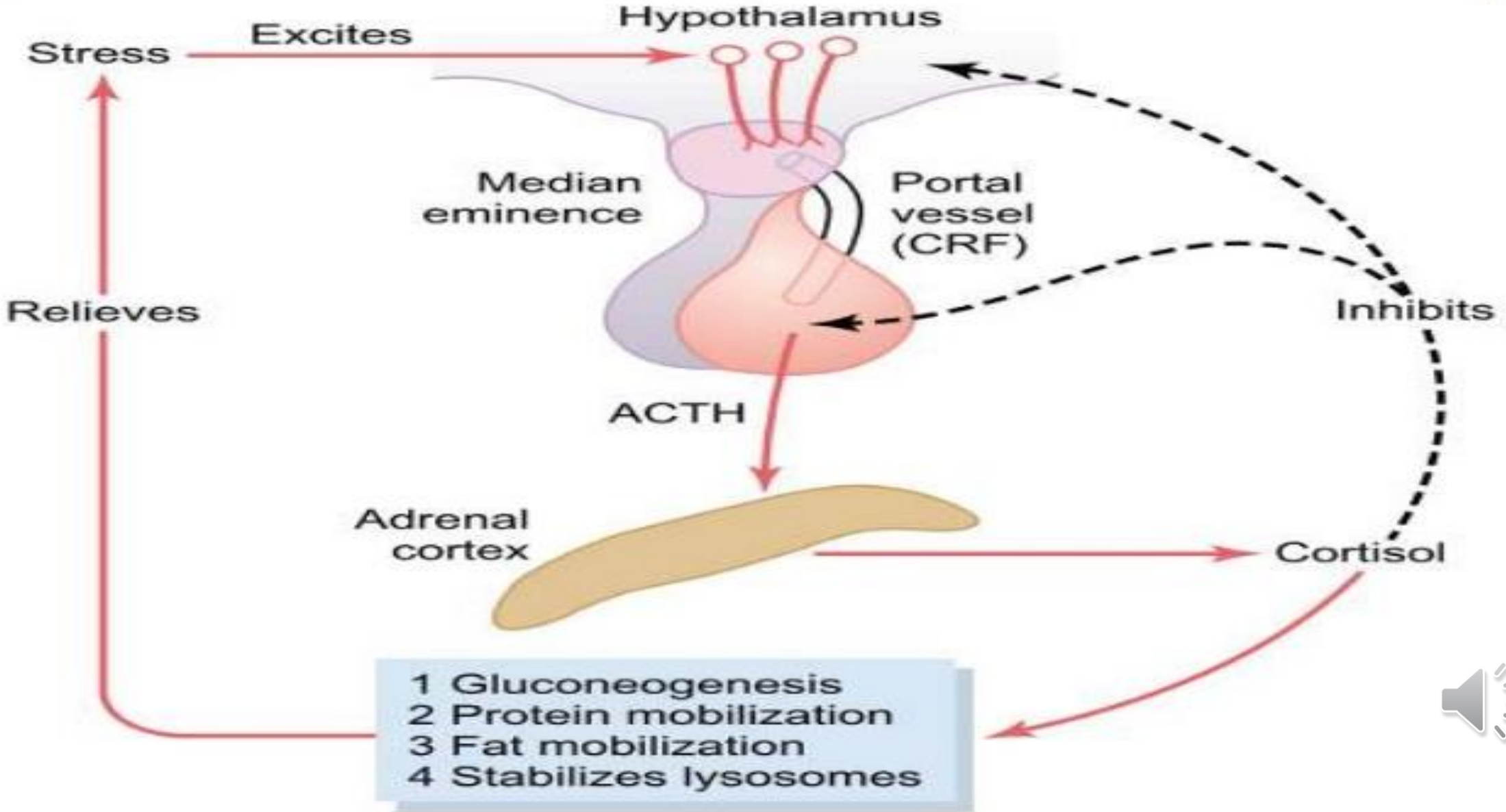
Introduction

- Cushing's syndrome (hypercortisolism) is a hormonal disorder caused by prolonged exposure **high levels of steroid hormones** called glucocorticoids.
- **Exogenous Cushing's syndrome**: caused by taking excessive amounts of medications e.g. prednisone, dexamethasone for chronic asthma, rheumatoid arthritis, lupus, to suppress immune system after transplant to prevent rejection, other inflammatory diseases.
  Endogenous Cushing's syndrome: excess cortisol produced by the adrenal glands. This is far rarer, but if left undiagnosed & untreated it can result in a shorter lifespan.

Pathophysiology

- Normally, the production and release of cortisol follows a precise chain of events. Corticotropin-releasing hormone (CRH) released from the hypothalamus causes the pituitary gland to secrete ACTH, which in turn results in the production of cortisol from the adrenal glands (located just above the kidneys).
- In healthy people, cortisol begins to rise between 3 and 4 am, reaches a peak between 7 and 9 am, and then falls for the rest of the day to the lowest levels when the person is unstressed and asleep at midnight.
- Cortisol controls its own production and release by switching off the hormones CRH and ACTH, a form of hormonal regulation known as “negative feedback”. ACTH and cortisol become elevated in response to stress, such as surgery, trauma, infection or other medical illnesses. i.e. Stress response

REGULATION OF CORTISOL SECRETION



Cortisol performs vital tasks in the body including:

helping maintain blood pressure and cardiovascular function

reducing the immune system's inflammatory response

balancing the effects of insulin, which breaks down glucose for energy regulating the metabolism of proteins, carbohydrates, and fats.

The problem occurs when the **negative feedback system** no longer works properly, due to malfunction of ACTH/ cortisol-releasing glands; or there is an artificial excess of cortisol in the body.

Causes:

Most commonly caused by prolonged use of **corticosteroid medications** for chronic illnesses such as asthma or rheumatoid arthritis.

Pituitary Adenomas

Pituitary adenomas cause 70 % of endogenous Cushing's syndrome cases.

Benign tumours of the pituitary gland: secrete extra ACTH. This form of the syndrome (**Cushing's disease**), affects women five times more often than men.

Ectopic ACTH Syndrome

Ectopic ACTH syndrome: benign/ cancerous tumours producing ACTH outside of the pituitary.

Lung tumors cause more than half of these cases, and men are affected three times more often than women.

Most common forms of ACTH-producing tumours: **small cell lung cancer**, (13% of all lung cancer cases)2 and **carcinoid tumours** (small, slow-growing tumours that arise from hormone-producing cells in various parts of the body).

Other less common types of tumors that can produce ACTH: **thymomas, pancreatic islet cell tumours**, and **medullary carcinomas of the thyroid**.

Adrenal Tumors

An abnormality of the adrenal glands- usually the presence of a tumour. Adrenal tumors are **four to five times more common in women than men.**

Average age of onset is about 40 yrs.

Most of these cases involve noncancerous tumours of adrenal tissue, **adrenal adenomas**, which release excess cortisol into the blood.

Adrenocortical carcinomas—adrenal cancers—are the least common cause of Cushing's syndrome. With adrenocortical carcinomas, cancer cells secrete excess levels of several adrenocortical hormones, including cortisol and adrenal androgens. **Usually cause very high hormone levels and rapid development of symptoms.**

Familial Cushing's Syndrome

Rarely, Cushing's syndrome results from an inherited tendency to develop tumours in one or more endocrine glands. e.g.With primary pigmented micronodular adrenal disease, children or young adults develop small cortisol-producing tumors of the adrenal glands. With multiple endocrine neoplasia type 1 (MEN1), hormone-secreting tumors of the parathyroid glands, pancreas, and pituitary develop.

Causes of endogenous Cushing's syndrome

Relative Frequency ACTH-producing pituitary adenoma (Cushing's Disease) 68%

Ectopic ACTH syndrome (bronchial, thymic, pancreatic, carcinoid tumours) 12%

Adrenal adenoma 10%

Adrenal carcinoma 8%

Ectopic CRH syndrome <1%

Macronodular hyperplasia, Micronodular hyperplasia 1%

Epidemiology

Cushing's syndrome is relatively rare; it affects approx of every million people each year.

It most commonly affects adults aged **20 to 50**.

People who are **obese and have type 2 diabetes**, along with poorly controlled blood glucose—also called blood sugar—and **high blood pressure**, have an increased risk of developing the disorder.

Signs & Symptoms Most people with Cushing syndrome will have:

Upper body obesity (above the waist)

and thin arms and legs Round

red, full face (moon face)

Slow growth rate in children

Skin changes that are often seen: Acne or skin infections

Purple marks (1/2 inch or more wide) called striae on the skin of the abdomen, thighs, and breasts

Thin skin with easy bruising

Muscle and bone changes include: Backache, which occurs with routine activities Bone pain or tenderness

Collection of fat between the shoulders (buffalo hump)

Thinning of the bones, which leads to rib and spine fractures

Weak muscles

Women with Cushing syndrome often have:

Excess hair growth on the face, neck, chest, abdomen, and thighs
Menstrual cycle becomes irregular or stops

Men may have: Decreased fertility ,Decreased or no desire for sex
Impotence

Other symptoms that may occur with this disease: Mental changes, such as depression, anxiety, or changes in behavior ,Fatigue, Headache
High blood pressure, Increased thirst and urination

DDX

*Sometimes other conditions have many of the same signs as Cushing's syndrome, even though people with these disorders do not have abnormally elevated cortisol levels.

E.g. **polycystic ovary syndrome** can cause menstrual disturbances, weight gain beginning in adolescence, excess hair growth, and impaired insulin action and diabetes.

Metabolic syndrome—a combination of problems that includes excess weight around the waist, high blood pressure, abnormal levels of cholesterol and triglycerides in the blood, and insulin resistance—also mimics the symptoms of Cushing's syndrome.

Diagnosis

- Diagnosis is based on a review of a person's medical history, a physical examination, and laboratory tests.
- X rays of the adrenal or pituitary glands can be useful in locating tumours. Tests to Diagnose Cushing's Syndrome **24-hour urinary free cortisol level**: Patient's urine is collected several times over a 24-hour period and tested for cortisol. **Levels higher than 50 to 100 micrograms a day** for an adult suggest Cushing's syndrome.
- **Midnight plasma cortisol** and **late-night salivary cortisol** measurements: The midnight plasma cortisol test also measures cortisol concentrations in the blood. Cortisol production is normally suppressed at night, but in Cushing's syndrome, this suppression doesn't occur. If the cortisol level is more than **50 nanomoles per litre (nmol/L),** Cushing's syndrome is suspected. The test generally requires a 48-hour hospital stay to avoid falsely elevated cortisol levels due to stress.

Screening test(cont)

- **Low dose/ overnight Dexamethasone suppression test**

Procedure:

- **Oral adm of 1 mg dexamethasone previous night and next day 8.00 am plasma cortisol < 5µg /d is normal and < 2µg/day excludes cushings syndrome.**
- **0.5mg dexamethasone 6 hourly for 2 consecutive day and plasma cortisol at 48 hrs < 5µg/dl is normal <2µg/dl excludes cushing's.**

Low-dose dexamethasone suppression test (LDDST):

- Patient is given a **low dose of dexamethasone (a synthetic glucocorticoid) orally every 6 hours for 2 days**. Urine is collected before dexamethasone is administered and several times on each day of the test. Cortisol and other glucocorticoids signal the pituitary to release less ACTH, so the normal response after taking dexamethasone is a drop in blood and urine cortisol levels**. If cortisol levels do not drop, Cushing's syndrome is suspected**.
- NB:The LDDST may not show a drop in cortisol levels in people with **depression, alcoholism, high estrogen levels, acute illness, or stress**, falsely indicating Cushing's syndrome.
- On the other hand, drugs such as phenytoin and phenobarbital may cause cortisol levels to drop, falsely indicating that Cushing's is not present in people who actually have the syndrome.
- For this reason, physicians usually advise their patients to stop taking these drugs at least 1 week before the test.

ESTABLISHING THE CAUSE

- **High-dose dexamethasone-suppression test**:
  - *Eight* doses of dexamethasone *2 mg* are given *orally* over *48 h*
  - There is *suppression* of serum cortisol in *pituitary dependent Cushing's disease* but not *in adrenal Cushing's or ectopic ACTH secretion*

- **Serum ACTH concentrations**:
  - *Elevated* concentrations are seen in *Addison's* disease, *adrenoleukodystrophy, Cushing's* disease, *ectopic* production of *ACTH* and *Nelson's* syndrome
  - *Low* concentrations are seen in *Cushing's* syndrome related to an *adrenal tumour, exogenous Cushing's* syndrome and *pituitary insufficiency*

Dexamethasone-corticotropin-releasing hormone (CRH) test:

- Some people have high cortisol levels but do not develop the progressive effects of Cushing's syndrome (e.g. muscle weakness, fractures, thinning of the skin).
- These people may have **pseudo-Cushing's syndrome**, a condition sometimes found in people who have depression or anxiety disorders, drink excess alcohol, have poorly controlled diabetes, or are severely obese. Pseudo-Cushing's does not have the same long-term effects on health as Cushing's syndrome and does not require treatment directed at the endocrine glands.
- The dexamethasone-CRH test rapidly distinguishes pseudo-Cushing's from mild cases of Cushing's.
- This test combines the LDDST and a CRH stimulation test. In the CRH stimulation test, an injection of CRH causes the pituitary to secrete ACTH. Pretreatment with dexamethasone prevents CRH from causing an increase in cortisol in people with pseudo-Cushing's. Elevations of cortisol during this test suggest Cushing's syndrome.

Prognosis If untreated, Cushing's syndrome can be life-threatening

If the cause can be treated, whether it means weaning the patient off cortisteroids, or surgically removing a tumour, the patient will fully recover.

Complications of untreated Cushing's syndrome include:

- Diabetes
- Enlargement of any tumours that are the underlying cause
- Fractures due to osteoporosis
- High blood pressure
- Kidney stones
- Serious infections

Treatment Cushing's syndrome caused by corticosteroid use:

- Slowly decrease the drug dose (if possible) under medical supervision. If you cannot stop taking the medication because of disease, high blood sugar, high cholesterol levels, and bone thinning or osteoporosis should be closely monitored.
- Cushing's syndrome caused by a pituitary tumour or tumour that releases ACTH: Surgery to remove the tumour Radiation after removal of a pituitary tumour in some cases (curative in 100% of patients with Cushing's disease) You may need hydrocortisone (cortisol) replacement therapy after surgery, and possibly continued throughout your life
- Cushing's syndrome due to an adrenal tumor or other tumors: Surgery to remove the tumour, followed by radiotherapy/ chemotherapy if required If the tumour **cannot be removed**, medications **to help block the release of cortisol**

Prevention

- Patients should be weaned off corticosteroid medication for their conditions as soon as possible.
- Awareness : early detection.

Thank you