

An Epidemiological Approach of ACTH Dependent Cushing's syndrome

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Abstract

Cushing's disease, or pituitary ACTH dependent Cushing's syndrome, is a rare disease responsible for increased morbidity and mortality. Signs and symptoms of hypercortisolism are usually nonspecific: obesity, signs of protein wasting, increased blood pressure, variable levels of hirsutism. Diagnosis is frequently difficult, and requires a strict algorithm. First-line treatment is based on transsphenoidal surgery, which cures 80% of ACTH-secreting microadenomas. The rate of remission is lower in macroadenomas. Other therapeutic modalities including anticortisol drugs, radiation techniques or bilateral adrenalectomy will thus be necessary to avoid long-term risks (metabolic syndrome, osteoporosis, cardiovascular disease) of hypercortisolism. This review summarizes potential pathophysiological mechanisms, diagnostic approaches, and therapies.

Introduction

Epidemiology

The incidence of Cushing's syndrome is estimated to be equal to 1–3 cases per million inhabitants per year, whereas its prevalence is close to 40 cases per million inhabitants. Of note, prevalence of hypercortisolism is thought to be equal to 2-5% of patients with poorly controlled diabetes and hypertension. Female preponderance is generally assumed to be close to 3:1 [2]. Cushing's disease is an extremely rare condition in children, with a peak in adults in the 3rd or 4th decade. Cushing's disease leads to death if untreated; it is responsible for increased morbidity and mortality, due to cardiovascular complications, infections and psychiatric disturbances [3,4].

Etiopathogenesis

Characteristics of corticotroph adenomas

Cushing's disease is frequently due to monoclonal benign and slow growing microadenomas (less than 10 mm) [9,10]. Plasma ACTH (and cortisol) classically lose their physiologic circadian periodicity. They are partially resistant to physiologic stimuli (*i.e.*, glucocorticoids), and do not respond to the normal feedback negative loop. In contrast, corticotroph adenomas are inappropriately sensitive to CRH and AVP. Altered CRH secretion as well as POMC qualitative changes in gene expression were also reported to be involved in the pathogenesis of Cushing's disease. Cushing's disease can be more atypical: secretion profiles are sometimes cyclic, with hypersecretion preceding a long period of normal secretion [8,11]. Some corticotroph adenomas are called "silent" as they are clinically and biologically comparable to non-secreting pituitary adenomas: diagnosis is made by the pathologist [12]. Finally, rare cases of aggressive pituitary adenomas or carcinomas have been reported [13]. Whether hyperplasia of corticotroph cells is or not a required initial step before the genesis of corticotroph adenoma remains a matter of debate. The origin of the disease, primary pituitary condition or secondary to an abnormality in the hypothalamus (chronic stimulation by CRH [14]), remains a matter of debate.

Potentially involved molecular mechanisms

Triggering signals leading to Cushing's disease remain unclear.

Oncogenes do not appear to be involved, as somatic mutations are usually not present in corticotroph adenomas cells. Recent studies in mice identified a potential role of loss of function of Brg1 (brahma-related gene 1) and HDAC2 (Histone Deacetylase 2) in the pathogenesis of Cushing's disease. Both proteins form a complex with the glucocorticoid receptor and the orphan nuclear receptor nuclear growth factor IB (NGFI-B) to repress POMC secretion. Interestingly, about 50% of corticotroph adenomas do not express these proteins anymore. The loss of Brg1 could lead to overexpression of cyclin E, leading to increased cell proliferation and sporadic hyperplasia or tumors. Interestingly, tumors with a loss of nuclear localization of Brg1 seem to be more responsive to anticortisol drugs *in vitro* compared to the ones with a complete loss of Brg1 oncogene [16,17].

Diagnosis

Diagnosis of Cushing's disease is difficult [20]. Clinical signs and symptoms are often non-specific; no single biological test combines optimal sensitivity and specificity for the diagnosis of hypercortisolism and for the determination of its etiology [21]. Moreover, pituitary and adrenal imaging can sometimes be confusing.

Several steps are needed to first confirm the diagnosis of hypercortisolism and then determine its origin: the first will be to confirm the lack of exposure to exogenous glucocorticoids that induces the same clinical characteristics as Cushing's syndrome and makes hypercortisolism screening unavailable [22]. In normal subjects, cortisol levels reach a peak at early morning and a nadir < 50 nmol/l around midnight. Patients with Cushing's syndrome lose this circadian rhythm. As a consequence, early morning ACTH and cortisol values are of poor diagnostic value in the screening methods of hypercortisolism. In contrast a midnight cortisol value > 200 nmol/l is strongly suggestive of Cushing's syndrome [23]. Evaluation of the circadian rhythm of cortisol is however not recommended as a first line screening method for hypercortisolism.

CRH test (100 µg intra-venously): more than 50% ACTH and 20% cortisol increase is in favor of Cushing's disease. Sensitivity and specificity are close to 90% [34].

Desmopressin test (10 µg intravenously), ACTH and cortisol increases similar to those observed with the CRH test are in favor of CD with 70% sensitivity and 85% specificity [20,35].

Concordant responses to at least 2/3 of these tests should lead to the diagnosis of Cushing's disease, and pituitary MRI. However, the sensitivity of MRI in CD is hardly greater than 60-70% and specificity close to 85%, as most corticotroph adenomas are microadenomas. In one study, 10% of the general population presented MRI pituitary images of less than 5 mm that might be considered as adenomas [36]. Cushing's disease diagnosis is thus confirmed in the presence of an adenoma > 6 mm and concordant responses to tests.

Clinical Management

Transsphenoidal surgery is the first line treatment of Cushing's disease [41,42]. It allows remission in 60-90% of microadenomas, and 50-70% of macroadenomas, depending on local invasion and the experience of the neurosurgeon [43-45]. Remission should be defined by normal ACTH and cortisol circadian rhythms, and suppressed cortisol value after overnight/low dose dexamethasone suppression test.

ACTH-lowering agents

Cabergoline is a dopamine agonist well known for its anti-secretory and anti-tumoral efficacy in prolactinomas. Corticotroph adenomas can express dopamine receptors. Recent studies reported that about 25% of patients treated by high doses of cabergoline for CD could be controlled as well [64-66]. A strict echocardiographic follow-up is required, due to a dose-dependent risk of valvulopathy.

Pasireotide is a somatostatin agonist with a particular binding affinity for somatostatin receptor (sstr) isoforms 1, 2, 3 and 5. This specific affinity for sstr5 could be of major interest in CD. Clinical trials are ongoing to determine efficiency of this drug. Preliminary results suggest that pasireotide is able to decrease cortisol levels in the majority of patients, but only few reach normalized values. There is a risk of induction or worsening of hyperglycemia in 1/3 cases [67-69].

Prognosis

The risks of chronic hypercortisolic state include excess morbidity and mortality due to increased cardio-vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome) leading to heart defect. Moreover, hypercortisolism is responsible for coagulopathy [77] and atherosclerosis [78], which also increase the risk to develop cardiovascular diseases. Recent data suggest that part of these defects due to hypercortisolism might remain after remission [78] even if the mortality rate would go back to normal [79]. Frequency of infectious diseases is also increased, as well as delayed healing. Hypercortisolism can induce severe osteoporosis in about 30% cases, and osteopenia in half of them. Also, acute cortisol excess can induce severe hypokalemia, as well as elevated blood pressure levels, and sometimes psychiatric signs [26,80]. Finally, more than half of patients with CS can present with psychiatric signs, from mild to severe depression, and cognitive dysfunction [81].

Pituitary Radiotherapy

Persistent hypercortisolemia after transsphenoidal surgery due to residual tumor can be treated with radiotherapy. Adjunctive medical control of hypercortisolemia may be needed while awaiting the effects of radiotherapy. Conventional fractionated radiotherapy is very effective, but its effects may be delayed up to 10 years, and it can be associated with long-term hypopituitarism.125 Stereotactic radiosurgery is more rapidly effective, but has been associated with a relapse rate of 20%.126.

Causes Cushing's syndrome

There are two types of Cushing's syndrome: *exogenous* and *endogenous*. The symptoms for both are the same. The only difference is how they are caused.

The most common is *exogenous* Cushing's syndrome and is found in patients taking cortisol-like medications such as prednisone. These medications are used to treat inflammatory disorders such as asthma and rheumatoid arthritis, or to suppress the immune system after an organ transplant. This type of Cushing's is temporary and goes away after the patient has finished taking the cortisol-like medications.

Endogenous Cushing's syndrome is rare, it usually comes on slowly and can be difficult to diagnose. It is caused either by a problem with the adrenal glands or the pituitary (a gland located at the base of the brain). In the adrenal glands, the problem is caused by a tumor (usually non-cancerous) that produces too much cortisol. When the problem is with the pituitary, the problem is caused by a tumor that produces too much ACTH (the hormone that tells the adrenal glands to make cortisol). When the tumors form in the pituitary the condition is often called *Cushing's disease*.

The majority of tumors that produce ACTH originate in the pituitary but sometimes non-pituitary tumors (usually in the lungs) can also produce too much ACTH and cause Cushing's syndrome.

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