DISEASE SUMMARY

**Definition**

*Cushing syndrome* is an endocrine disease with multiple etiologies and is characterized by a constellation of clinical manifestations that result from excessive concentrations of circulating cortisol (i.e., hypercortisolism). The syndrome is named after Harvey Cushing, an American surgeon who first reported the condition in 1912.

**Prevalence**

By far, the single most common cause of Cushing syndrome today (as many as 12 cases/1 million people) is the use of corticosteroid medications to treat a wide variety of disease states, including rheumatoid arthritis, asthma, and multiple sclerosis. The prevalence of hypercortisolism from all other causes combined is only 13 cases per 1 million people nationally. The overall incidence is estimated as 2 new cases per 1 million persons per year.

Females are eight times more likely than males to develop hypercortisolism from a pituitary tumor and three times more likely to develop a cortisol-secreting adrenal tumor. However, hormone-producing lung tumors that cause hypercortisolism are more common in males.

Ninety percent of all cases of Cushing syndrome occur during adulthood. The incidence of Cushing syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year. The peak incidence of Cushing syndrome due to an adrenal or pituitary tumor occurs in persons 25–40 years of age.

**Significance**

The significance of Cushing syndrome lies primarily in the multitude of complications that can result from hypercortisolism. Some complications are cosmetic (e.g., moon-shaped face and stretch marks), others are purely bothersome (bruising with minimal trauma), some cause pain (e.g., osteoporosis), and still others are potentially life-threatening (e.g., hypertension, diabetes mellitus, and susceptibility to serious infections). Cushing syndrome has various causes and the patient's prognosis depends on the specific etiology of elevated corticosteroids. Based on cause, the prognosis ranges from excellent (e.g., drug-induced Cushing syndrome, which is reversible with discontinuation of the drug) to poor (e.g., cortisol-producing adrenal gland cancer, which has a median survival time of only 7 months).
**Causes and Risk Factors**

Causes of Cushing syndrome are typically divided into two basic categories: those that are adrenocorticotropic hormone (ACTH)-dependent (i.e., hypercortisolism is the result of elevated serum ACTH concentrations) and those that are ACTH-independent. The majority of cases diagnosed today are the result of administering supra-physiologic doses of corticosteroid drugs for various health conditions (e.g., autoimmune disease). Common corticosteroids prescribed include prednisone, prednisolone, and methylprednisolone. This type of Cushing syndrome is often referred to as iatrogenic Cushing syndrome and is a reversible form of the disorder. Clinical manifestations are dose-dependent, and low-dose administration may not cause visible signs of hypercortisolism.

Cases of pathologic Cushing syndrome are less common and include the following:

* hypersecretion of ACTH by a small, benign pituitary tumor known as an adenoma. This is commonly known as Cushing disease and is the most common cause of pathologic Cushing syndrome.
* hypersecretion of ACTH by non-pituitary tumors (e.g., small cell lung carcinoma). This is known as ectopic Cushing syndrome because the source of ACTH technically lies outside of the neuroendocrine system.
* hypersecretion of cortisol from either a benign or a cancerous tumor (carcinoma) of the adrenal gland
* hypersecretion of corticotropin-releasing hormone (CRH) by a benign tumor of the hypothalamus. Excessive circulating CRH causes excessive secretion of ACTH by the pituitary and, ultimately, elevates serum cortisol levels.

**Pathophysiology**

In patients suffering from hypercortisolism that is ACTH-independent, clinical manifestations are primarily the result of excessive concentrations of circulating corticosteroids (e.g., cortisol). Excessive cortisol has the following adverse effects:

* increase in appetite and promotion of fat deposition in the face (full moon-shaped face), back of the neck (so-called “buffalo hump”), and around the waist (truncal obesity)
* increase in blood glucose levels by promoting hepatic gluconeogenesis and inhibiting glucose uptake by muscle and adipose tissue (i.e., causes insulin resistance and diabetes mellitus)
* inhibition of both immune and inflammatory reactions that creates a susceptibility to infections (particularly fungal infections). Cortisol specifically acts in this manner by decreasing T lymphocyte proliferation and suppressing the synthesis of important chemical mediators of inflammation (e.g., prostaglandins and leukotrienes).
* sensitization of α-adrenergic receptors on the surface of smooth muscle cells in arterioles and enhancement of the vasoconstrictive effects of circulating catecholamines, leading to an elevation in blood pressure
* increase in protein catabolism, resulting in protein wasting in muscles of the extremities (causing muscle atrophy), bone (leading to osteoporosis and pain), skin (resulting in thin skin and stretch marks), and blood vessel walls (causing rupture with minimal trauma)
* neuronal function depression, resulting in significant mood changes that include major depression and schizophrenia

In patients with hypercortisolism that is ACTH-dependent, hyperpigmentation of the skin and gums may occur (because ACTH indirectly stimulates melanin synthesis). In addition, serum androgen levels may increase significantly (because ACTH stimulates androgen synthesis in the adrenal gland). This latter pathophysiologic effect is especially problematic in females, who may suffer from excessive hair growth (especially facial hair), a more masculine-sounding voice, acne (which can be androgen-induced), and decreased blood flow during menses. If serum aldosterone is also significantly elevated, weight gain and blood pressure elevation from sodium and water retention may occur. Excessive aldosterone levels may also induce a hypokalemic alkalosis (i.e., low serum K⁺ and H⁺) in the patient.
Diagnosis: Clinical Manifestations and Laboratory Tests

Patients with Cushing syndrome often have the following clinical manifestations:

- round, full, moon-shaped face
- collection of fat in the cervical area and abdomen
- thin arms and legs
- elevated blood pressure
- back pain
- striae (stretch marks), especially in the thighs, breasts, and abdomen
- wide range of mental symptoms from an inability to concentrate to severe psychosis

Patients are also highly susceptible to developing acne, superficial skin infections, bruises, and glucose intolerance—which is manifested by excessive thirst (polydipsia), excessive glucose in the blood (hyperglycemia) and urine (glycosuria), and frequent urination (polyuria). Females may also suffer from signs of androgen excess, such as amenorrhea and hirsutism.

In patients with ACTH-dependent disease, serum ACTH, cortisol, and androgen concentrations are elevated (as is, in some cases, serum aldosterone). In patients with ACTH-independent disease, serum cortisol levels are high but serum ACTH concentrations are low (due to negative feedback of cortisol on the hypothalamus and anterior pituitary gland) and serum aldosterone is normal.

A midnight serum cortisol level >7.5 µg/dL or a midnight salivary cortisol level >550 ng/dL is highly suggestive of Cushing syndrome. An abnormally high 24-hour urine-free cortisol (by high-performance liquid chromatography) after receiving 1 mg dexamethasone orally late the previous evening, Cushing syndrome can be ruled out with 98% certainty. Once hypercortisolism is established, a baseline plasma ACTH is obtained. A low ACTH level indicates ACTH-independent disease, while an elevated ACTH concentration is consistent with ACTH-dependent Cushing syndrome.

With ACTH-dependent Cushing syndrome, an MRI scan of the pituitary will demonstrate a small, benign tumor in approximately half of all patients. Location of ectopic sources of ACTH is accomplished with computed tomography (CT) scans of the chest and abdomen. ACTH-secreting tumors are often discovered in the lungs, thymus gland, or pancreas. In most cases of ACTH-independent disease, a CT scan of the adrenal will help to identify a tumor. Disease Summary Figure 52.1 illustrates many of the potential clinical manifestations of Cushing syndrome/disease.

Appropriate Therapy

Treatment for Cushing syndrome is dependent on the specific cause of the disease. Many of the clinical manifestations of drug-induced Cushing syndrome resolve when medication is discontinued. However, to prevent an acute episode of adrenal insufficiency, the corticosteroid medication must be tapered.

Cushing disease is best treated with surgical removal of the pituitary tumor and long-term hydrocortisone replacement therapy (6–36 months) until ACTH-secretory function recovers. The cure rate approaches 90%. Another treatment option is gamma knife radiosurgery, which normalizes cortisol levels in two thirds of patients within 1 year. Conventional radiation therapy is only curative in approximately one in four patients, but provides an option for patients who are not good surgical candidates.

Adrenal neoplasms secreting cortisol are resected laparoscopically. Adrenal carcinomas that have spread outside the adrenal gland are treated systemically with the anticancer drug mitotane. Ectopic ACTH-secreting tumors should also be surgically removed. If tumors cannot be resected, laparoscopic removal of both adrenal glands is recommended. When patients are not good candidates for surgery, a pharmacologic approach may be tried. Ketoconazole may be used to suppress cortisol synthesis, but liver enzymes must be monitored for hepatotoxicity. Metyrapone also inhibits cortisol synthesis but may promote masculinizing effects in females. When given parenterally, the somatostatin analog octreotide suppresses ACTH secretion in approximately one third of cases.
Serious Complications and Prognosis

Major causes of death include overwhelming infection, suicide secondary to major depression, and complications resulting from hypertension (e.g., heart failure and stroke).

Prognosis varies from poor to excellent and also depends on the specific cause of hypercortisolism. Since the patient with iatrogenic Cushing syndrome often develops adrenal cortical atrophy with virtually no source of natural cortisol, sudden discontinuation of corticosteroid
medications may result in a life-threatening episode of acute adrenocortical insufficiency characterized by shock. With slow tapering of corticosteroid doses, symptoms resolve and prognosis is excellent.

Following a successful adrenalectomy, patients with a benign adrenal tumor have a 95% 5-year survival rate and a 90% 10-year survival rate. Surgery for pituitary tumors may have a rate of failure as great as 20%. However, if surgery is successful, the 5-year survival rate exceeds 90%. The prognosis for patients with ectopic ACTH-secreting neoplasms depends on the specific type of tumor and its extent of spread. The 2-year survival rate for small cell lung carcinoma (a common ectopic source of ACTH hypersecretion) is very poor: 20% when confined to the lung and only 5% with dissemination. Patients with ACTH secretion from an unknown source have a 5-year survival rate of 65% and a 10-year survival rate of 55%. Finally, the median survival time for patients with cortisol-secreting adrenal cancer (carcinoma) is only 7 months.

**Suggested Readings**


