Cushing’s Syndrome

Description/Etiology
Cushing’s syndrome (CS) is a rare endocrine disorder caused by chronic exposure of the body’s tissues to excess exogenous or endogenous cortisol (i.e., hypercortisolism). In Cushing’s disease, the leading cause of CS, a pituitary gland tumor (usually a microadenoma) releases excessive amounts of adrenocorticotropic hormone (ACTH), which stimulates excessive adrenal gland cortisol release. Nonpituitary causes of CS include ectopic ACTH syndrome, which occurs when tumors that form outside the pituitary gland produce excess hormone. ACTH–independent CS may also be caused by prolonged use of exogenous glucocorticoid steroid treatment for inflammatory diseases and adrenal adenomas.

In addition to the endocrine system, CS affects the musculoskeletal, skin/exocrine, and cardiovascular systems. The classical description of the syndrome includes central obesity (i.e., abdominal obesity), hypertension, abdominal purple striae, hypokalemia, unexplained osteoporosis, and glucose intolerance. CS is diagnosed based on clinical findings confirmed by lab results of inappropriately elevated serum, salivary, or urine cortisol levels; CS must be differentiated from hypercortisolism (called pseudo-Cushing’s syndrome) secondary to alcoholism or other stressful events such as pregnancy, depression, intense exercise, critical illness and uncontrolled diabetes mellitus. The usual course of CS is chronic, with cyclic exacerbations and rare remissions.

Treatment depends on the primary cause of the syndrome, the certainty of the diagnosis, and the expertise of the care team, and includes pharmacotherapy and surgery: transsphenoidal adenomectomy for pituitary adenomas; bilateral adrenalectomy and/or surgical removal of other ectopic ACTH-secreting tumors; radiotherapy, stereotactic radiotherapy, or immunotherapy, generally reserved for children and for patients not cured by transsphenoidal surgery; and total bilateral adrenalectomy, reserved for patients not cured by transsphenoidal surgery or pituitary irradiation. Lifelong cortisol replacement therapy may be necessary. The prognosis depends on the cause, and may be favorable with surgical intervention. CS caused by adrenocortical carcinoma is associated with a poor prognosis.

Facts and Figures
CS is relatively rare, affecting 13/1,000,000 people per year. CS can occur at any age, but most commonly occurs in adults between the ages of 25 and 40 years. It is more common in women than men (5-8:1). Cushing’s disease accounts for 80–85% of cases of CS and pituitary adenomas are the cause of 80–90% of cases of Cushing’s disease. Screening studies of obese patients diagnosed with type 2 diabetes indicated that the prevalence of CS is 2–5%. (Bansal et al., 2015; Resmini, 2014)

CS remission rate following pituitary surgery is 40–90%, whereas the duration of remission ranging from 3.4–11.9 years. CS mortality rate is four times higher than the general population. (Daniel et al., 2015; Andela et al., 2015)

Risk Factors
Risk factors for CS include female sex, administration of exogenous steroids (e.g., to treat a variety of rheumatologic [e.g., rheumatoid arthritis], pulmonary [e.g., asthma], neurological, and nephrotic diseases or to prevent rejection in organ transplant recipients). Individual
who are genetically predisposed to develop tumors of the endocrine glands (e.g., individuals with Carney complex or McCune-Albright syndrome) are at risk for CS.

**Signs and Symptoms/Clinical Presentation**

Symptoms include ruddy complexion, increased facial or body hair in women, obesity, rounded face, fatigue, muscle weakness, backache, headache, polyuria, depression, emotional lability, cognitive impairment, anxiety, easy bruising, menstrual irregularities, and skeletal growth retardation in children. Complications of CS include bone fractures, osteoporosis, hypertension, increased susceptibility to infection, diabetes mellitus, kidney stones, peptic ulcers, and distant metastases. In men, decreased fertility, impotence, and decreased libido are common. Fertility is impaired in young women diagnosed with CS, though they may become pregnant while taking medical treatment.

**Assessment**

› **Physical Findings of Particular Interest**
  * A clinician may observe darkened skin on the neck (i.e., acanthosis); increased adiposity of the face (i.e., moon face), neck, and trunk; fat pad accumulation over the upper back and trunk (i.e., buffalo hump); and/or red to purple striae on the skin

› **Laboratory Tests That May Be Ordered**
  * Urinary free cortisol (UFC) over a 24-hour period may be elevated (e.g., > 100 micrograms per day in adults), indicating CS (i.e., remains the gold–standard confirmatory test)
  * Late night (e.g., 11 P.M.) salivary cortisol levels may be elevated and represent a convenient method to screen for and diagnose CS
  * Dexamethasone suppression test (DST) will identify changes in 24-hour plasma cortisol and urinary free cortisol levels; increased cortisol levels indicate CS, decreased levels indicate Cushing’s disease (see Red Flags, below)
  * Corticotrophic-releasing hormone (CRH) stimulation test with hormone injections shows increased blood levels of ACTH and cortisol in patients with Cushing’s disease; typical blood level increases in CS are limited to cortisol
  * Inferior petrosal sinus sampling distinguishes pituitary causes from ectopic causes of CS
  * Dexamethasone-CRH test (i.e., a test that combines the DST and CRH stimulation test measurement over a 48-hour period) differentiates CS from pseudo-Cushing’s; a cortisol level higher than 50 nmol/L (1.4 mcg/dL) identifies CS
  * Metyrapone testing shows increased plasma levels of 11-deoxycortisol in CS and Cushing’s disease
  * Urinary prostate specific antigen (PSA) may be elevated in women with CS (Wu et al., 2011)
  * CBC may show increased WBCs and decreased lymphocytes; serum chemistry may show increased glucose and cholesterol, decreased potassium and chloride, and metabolic alkalosis; and urinalysis may show increased urine glucose in CS

› **Other Diagnostic Tests/Studies**
  * X-rays of the lumbar spine may show osteoporosis; ultrasonography, chest and abdominal CT scan (i.e., most ectopic ACTH sources originate in the lungs), and angiography may show adrenal tumors; and cranial CT scan or MRI may show pituitary tumors
  * If imaging studies are negative, an Inferior Petrosal Sinus sampling (IPS) may be ordered (i.e., catheters are placed in the petrosal sinuses to obtain sampling that might indicate whether the pituitary is the source of ACTH hypersecretion)

**Treatment Goals**

› **Promote Optimum Physiologic Function and Reduce Risk of Complications**
  * Monitor vital signs, especially BP; assess for signs and symptoms of underlying disease/condition (e.g., abdominal distension, adrenal hypofunction symptoms of orthostatic hypotension, apathy, weakness) and review laboratory/diagnostic study results
    – Report abnormalities and treat, as ordered, especially hypertension, edema, infection, diabetes, and cardiovascular compromise in potential surgery patients; medications that may be ordered include antihypertensives, calcium supplementation and bisphosphonates for osteoporosis, vasopressors to decrease shock risk, and anti-anxiety agents or sedatives to reduce anxiety
  * Frequently assess for pain, nausea, vomiting, diarrhea, and neurological and behavioral changes; provide symptomatic relief, as ordered. Monitor intake and output
  * Assess for cognitive compromise and increased fall risk; maintain patient safety (e.g., airway, circulation, and prevention of injury) and supervise all ambulation
• Administer prescribed pharmacologic treatment of adrenal steroid inhibitors (e.g., ketoconazole, aminoglutethimide) and, if necessary to avoid subsequent adrenal insufficiency, glucocorticoid replacement therapy (e.g., prednisolone, cortisone acetate); monitor treatment efficacy and for adverse effects, or overtreatment (e.g., drop in blood pressure when the patient stands up, hypoglycemia, sweating, irritability, depression)
• Follow facility pre- and posttreatment protocols if patient becomes a surgical candidate (e.g., for tumor removal) or radiotherapy candidate; reinforce pre- and posttreatment education and verify completion of facility informed consent documents
  – Administer cortisol therapy, as ordered, to surgical candidates to prevent postsurgical adrenal hypofunction
  – Closely monitor for posttreatment complications
• Request referral to physical therapy for development of an exercise regimen; provide a diet high in protein and potassium and low in calories, carbohydrates, and sodium; request referral to a dietitian for patient education on nutrition
  › Promote Emotional Well-Being and Educate
    • Assess anxiety level, emotional lability, and coping ability; educate and encourage discussion about CS pathophysiology, treatment risks and benefits, and prognosis

Food for Thought
› Pasireotide (Signifor) is a somatostatin analogue that was approved by the U.S. FDA in 2012 for treatment of patients with Cushing’s disease who cannot undergo surgical resection of the pituitary adenoma
› Schizophrenia can be the initial presentation of CS, but may improve after excess cortisol is reduced. Nonetheless, psychopathology and impaired quality of life occur in about 25% of the cured CS patients
› In a study done in India researchers found that yoga may affect the hypothalamus with an anti-stress effect, thus reducing cortisol levels and bring relief for depression, a common sign in Cushing’s disease

Red Flags
› DST results can be false-positive due to depression, alcohol abuse, high estrogen levels, acute illness, and stress, and false-negative due to medications (e.g., phenytoin, Phenobarbital)
› Monitor intensively for signs of increased intracranial pressure or hypopituitarism (i.e., inadequate secretion of one or more pituitary hormones) after pituitary surgery
› Emphatically warn the patient against abrupt discontinuation of steroid medications because it may produce a fatal adrenal crisis
› Supervise all ambulation; patients with CS are at greatly elevated risk of pathologic fracture
› Pituitary tumors and ectopic tumors are often too small to be visualized with even the most sophisticated imaging techniques

What Do I Need to Tell the Patient/Patient’s Family?
› Educate about the prescribed medication regimen; advise patient to immediately report adverse effects, avoid excessive corticosteroid treatment, and take antacids with meals to minimize gastric irritation
› Advise patient to wear a Medic Alert bracelet or pendant; closely watch for signs of adequate steroid dosage (e.g., fatigue, weakness, and dizziness) and excessive steroid dosage (e.g., severe edema and weight gain); accident proof the home and wear seat belts to prevent fractures and other injuries; and seek immediate medical attention for new or worsening signs and symptoms

References


