Cushing Syndrome

Jason Klein, MD, Patricia Vuguin, MD, MSc, Sharon Hyman, MD
Department of Pediatric Endocrinology, Cohen Children's Medical Center of New York, New Hyde Park, NY

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Cushing syndrome (CS) is a state of glucocorticoid excess in which there is loss of the normal hypothalamic-pituitary-adrenal feedback axis. First described in 1912 by American neurosurgeon Dr Harvey Williams Cushing in reference to a 23-year-old patient with obesity, hirsutism, and amenorrhea, CS has since been recognized as a rare, yet serious and significant, condition in the pediatric population.

Under normal circumstances, hypothalamic corticotropin-releasing hormone (CRH) is delivered to the anterior pituitary via the portal circulation, resulting in adrenocorticotropin hormone (ACTH) release from the anterior pituitary into the systemic circulation. ACTH acts on the zona fasciculata of the adrenal cortex to stimulate release of cortisol. The secretion of cortisol results in negative feedback, downregulating production of both ACTH and CRH. Cortisol has metabolic and cardiovascular effects. It plays an important role in hepatic glucose metabolism by increasing gluconeogenesis and glycogenolysis, as well as affecting proteolysis and lipolysis. In addition, it influences myocardial contractility, cardiac output, and blood pressure. It also has a variety of effects on the immunologic and inflammatory systems, musculoskeletal and connective tissue, and fluid and electrolyte homeostasis, as well as neuropsychiatric, behavioral, gastrointestinal, and developmental effects. In the general population, there are approximately 2 to 5 new cases per million per year of CS; only approximately 10% of these cases occur in the pediatric population. Although adolescents with CS, similar to adults, have a slight female to male predominance, this predilection goes away in younger patients and may even be reversed in infants with CS.

Pediatric CS can be divided into 2 distinct categories: ACTH dependent and ACTH independent (Table 1). The most common cause of CS is exogenous administration of corticosteroids, which have become the first-line treatment of multiple pediatric disorders. Although oral corticosteroids are generally implicated in the development of CS, long-term use of inhaled and topical corticosteroids, commonly used as treatment for asthma and atopic dermatitis, respectively, can also result in CS. In addition, ACTH, used as treatment in certain seizure disorders, can stimulate adrenal cortisol release, resulting in CS.

When exogenous causes of CS have been ruled out based on a careful history, endogenous causes should be sought. In children older than 5 years, Cushing disease (hypercortisolism resulting from oversecretion of pituitary ACTH from a corticotroph adenoma) is the most common cause of CS. In contrast, infants are most likely to have a primary adrenal condition, such as an adrenocortical tumor (adenoma or carcinoma). Although adrenocortical tumors are fairly rare in the pediatric age group, comprising only approximately 0.6% of childhood tumors, upward of one-third manifest with signs and symptoms of CS. Nearly all are unilateral (90% to 98%) and more than 70% are malignant. Most unilateral adrenal tumors are sporadic, but they may be part of a genetic syndrome, such as Beckwith-Wiedemann syndrome or Li-Fraumeni syndrome.

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TABLE 1. **Categories of Pediatric Cushing Syndrome**

ACTH-DEPENDENT CUSHING SYNDROME	ACTH-INDEPENDENT CUSHING SYNDROME
Exogenous ACTH use	Exogenous corticosteroid use
Cushing disease (ACTH-secreting pituitary adenoma)	Adrenocortical tumor
Ectopic ACTH syndrome (ACTH-secreting disease from nonpituitary site)	Bilateral primary adrenocortical hyperplasia PPNAD or Carney complex Massive macronodular adrenal hyperplasia McCune-Albright SYNDROME
CRH hypersecretion (adult case reports only)	

ACTH=adrenocorticotropin hormone; CRH=corticotropin-releasing hormone; PPNDAD=primary pigmented nodular adrenocortical disease.

Rarer causes of ACTH-independent CS include primary pigmented nodular adrenocortical disease, a condition characterized by bilateral nodular adrenals. Primary pigmented nodular adrenocortical disease is associated with atypical or cyclical CS and is the most frequent presentation of Carney complex in children and adolescents, characterized by skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, and schwannomas. Massive macronodular adrenal hyperplasia is rare and associated with extremely large adrenals and multiple cortisol-producing adenomatous nodules. McCune-Albright syndrome, a triad of precocious puberty, cafe-au-lait spots, and polyostotic fibrous dysplasia, can result in continually activated, ACTH-independent cortisol release.

In ACTH-dependent CS, ectopic ACTH release by certain tumors, such as squamous cell carcinoma of the lung and neuroendocrine masses, is an infrequent cause of CS, representing only approximately 1% of cases of pediatric CS.

The classic signs and symptoms of CS (Table 2) tend to be insidious in development and are not always all present. By far, the most common presentation in pediatrics is growth failure in association with excessive weight gain, present in nearly 90% of cases. Review of growth curves in the preceding years is a crucial step in the workup of CS. Because exogenous obesity is associated with tall stature and robust growth velocity, evaluation for CS should be considered in any patient with poor growth velocity with increased weight gain. Hirsutism and acne are common, as well as irregular menses in adolescent girls. Buffalo hump, from an increased dorsocervical fat pad, and/or moon facies may be seen in three-quarters of patients. Osteopenia tends to be subclinical and is likely underdiagnosed, although bone mineral density is regained after adequate treatment of CS. Hypertension, especially elevation of diastolic blood pressure, occurs in approximately half of pediatric patients with CS.

The initial step in making the diagnosis of CS is confirming the presence of elevated cortisol levels (hypercortisolism) in 2 separate measurements. Screening tests, particularly when in conjunction with each other, have a high sensitivity and sensitivity for detecting CS. Twenty-four-hour urine

TABLE 2. **Signs and Symptoms of Cushing Syndrome**

SIGN OR SYMPTOM	PATIENTS AT PRESENTATION, %
Weight gain	90
Growth failure	83
Hirsutism or acne	78
Amenorrhea and delay puberty	78
Generalized for centripetal obesity (buffalo hump or moon facies)	75
Osteopenia	70
Violaceous striae (may be hyperpigmented when ACTH level is elevated)	60
Hypertension	50
Headaches	25
Plethora and skin bruising	25
Compulsive behaviors and emotional lability (depression)	20
Muscle weakness	12

ACTH=adrenocorticotropin hormone.

collection for free cortisol has been used since the 1970s, with levels greater than 90 μg/24 h (via radioimmunoassay) consistent with hypercortisolism, although ensuring adequate collection is difficult and cumbersome. Because CS is associated with loss of the normal diurnal pattern of cortisol secretion, abnormally elevated levels of cortisol should be expected around midnight, the time of the normal nadir. A midnight salivary cortisol sample has a near 100% sensitivity and 96% specificity for CS when the level is greater than 0.13 μg/dL (3.6 nmol/L). An overnight low-dose dexamethasone suppression test (1 mg given orally between 11 PM and midnight) should normally result in a low 8 AM cortisol level the next morning; a cortisol level greater than 1.8 μg/dL (49.7 nmol/L) despite dexamethasone suppression has a 95% sensitivity for CS but a lower specificity of approximately 80%.

Once elevated cortisol levels have been confirmed, the next step in diagnosis is to determine whether the hypercortisolism is under hormonal control from ACTH secretion. This is best accomplished with a plasma ACTH sample drawn between 11 PM and 1 AM: a level greater than 23 pg/mL (5 pmol/L) in a patient with hypercortisolism confirms ACTH dependency. By comparison, patients with primary adrenal CS tend to have virtually undetectable ACTH levels (<5 pg/mL [1 pmol/L]), and those with ectopic ACTH syndrome have levels elevated upward of 100 times normal.

After biochemical confirmation of CS, imaging plays an important role in the next steps of management. In patients with laboratory findings consistent with ACTH-dependent CS or Cushing disease, contrast-enhanced magnetic resonance imaging of the pituitary should be performed, looking for a corticotroph microadenoma. In the absence of an obvious pituitary mass on imaging, inferior petrosal sinus sampling may be necessary to localize and lateralize a small microadenoma. For investigation of ACTH-independent CS from a primary adrenal tumor or bilateral nodular adrenal disease, adrenal computed tomography is the imaging study of choice. Adrenal carcinomas tend to be large at diagnosis, whereas adrenocortical adenomas are typically smaller than 5 cm in diameter; both tend to be unilateral but rarely are bilateral. Imaging for the workup of ectopic ACTH syndrome may include computed tomography, magnetic resonance imaging, positron emission tomography, and/or octreotide scanning.

For ACTH-dependent pituitary adenomas, transsphenoidal resection by an experienced neurosurgeon is the treatment of choice. A successful cure rate is 80% to 90% on the first surgery, with decreasing rates of cure on subsequent attempts. Surgical complications, such as diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, panhypopituitarism, bleeding, and pituitary apoplexy, are rare but can occur. For a unilateral adrenal mass, single adrenalectomy has a nearly 100% cure rate; a few require adjunctive chemotherapy. With the bilateral nature of nodular disease, which fortunately is rare, both adrenal glands may have to be removed to ensure cure. In cases of surgical failure or ectopic ACTH secretion without a localized source, some pharmacotherapeutic options exist; mitotane, for example, inhibits the production of corticosteroids by blocking essential enzymes and destroying adrenocortical cells.

Once treatment for CS has been started and glucocorticoid levels suddenly decrease, affected patients are at risk for adrenal crisis if replacement glucocorticoid therapy at stress doses (approximately 3 times daily maintenance in 3 to 4 divided oral doses) is not started. This regimen can subsequently be weaned to maintenance level (6 to 9 mg/m^2 daily in 2 to 3 divided oral doses), followed by an ACTH-stimulation test to assess the integrity of the hypothalamic-pituitary-adrenal axis.

COMMENT: Our authors note that the most common cause of CS is the administration of exogenous steroids. With a prevalence of close to 10% among children in the United States, asthma is the most common diagnosis for which our patients receive corticosteroids, both orally and inhaled. The Centers for Disease Control and Prevention has reported that although the prevalence of asthma has increased since the turn of this century, health care visits for asthma per 100 persons with asthma have decreased in primary care settings, and asthma is disproportionately prevalent among children who are least likely to have ongoing medical care. Episodic visits for emergency treatment, with the possibility of additional courses of rescue steroids without consistent monitoring, are not the way to prevent glucocorticoid toxicity.

– Henry M. Adam, MD
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