Cushing's Syndrome in Pediatrics: An Update

Maya B. Lodish, MD, MHSc, Margaret F. Keil, PhD, CRNP*, Constantine A. Stratakis, MD, D(Med)Sci

KEYWORDS

• Cushing's syndrome • Pituitary tumors • Adrenal cortex • Carney complex
• Adrenocortical hyperplasia • Adrenal cancer

KEY POINTS

- Cushing's syndrome in childhood results mostly from the exogenous administration of glucocorticoids; endogenous Cushing's syndrome is a rare disease.
- In childhood, lack of height gain concomitant with weight gain is the most common presentation of Cushing's syndrome.
- The first step in the diagnosis of Cushing's syndrome is documentation of hypercortisolism with the 24-hour urinary free cortisol, late-night salivary cortisol, or a low-dose dexamethasone-suppression test.
- In children older than the age of 6 years, Cushing's syndrome is most commonly caused by a corticotropin-secreting pituitary tumor, in children less than 6 years old, adrenal causes are more common etiologic factors of Cushing's syndrome.
- When the diagnosis of Cushing's syndrome is confirmed, algorithms for testing to distinguish corticotropin-dependent disease from the corticotropin-independent syndrome are available. Surgery is the first-line treatment intervention.

EPIDEMIOLOGY AND ETIOLOGIC FACTORS

Endogenous Cushing's syndrome (CS) is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol, whether due to corticotropin-dependent or corticotropin-independent cause. In contrast, exogenous or iatrogenic CS occurs when glucocorticoids in the form of medications, such as prednisone, which are commonly used for inflammatory disorders, are given in high enough doses for prolonged periods of time. The overall incidence of endogenous CS is 0.7 to 2.4 per million people per year.[1] Only approximately 10% of the new cases

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Section on Endocrinology and Genetics, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), NIH-Clinical Research Center, 10 Center Drive, Building 10, Room 1E-3330, MSC1103, Bethesda, MD 20892, USA
* Corresponding author.
E-mail address: keilm@mail.nih.gov

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each year occur in children. In both adults and children, CS is most commonly caused by a corticotropin-secreting pituitary tumor.

Under normal conditions cortisol is secreted from the cortical cells of the adrenal glands under the control of the pituitary hormone corticotropin (adrenocorticotropic hormone). Corticotropin-releasing hormone (CRH) is synthesized in the hypothalamus and carried to the anterior pituitary in the portal system. CRH stimulates adrenocorticotropic hormone (corticotropin) release from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol (hypothalamic-pituitary-adrenal [HPA] axis).[2,3] Cortisol primarily inhibits the secretion of CRH and, secondarily, corticotropin in a negative feedback regulation system. In CS, the HPA axis has lost its ability for self-regulation owing to excessive secretion of either corticotropin or cortisol, and the loss of the negative feedback function. Diagnostic tests, on the other hand, take advantage of the tight regulation of the HPA axis in the normal state and its disturbance in CS to guide therapy toward the primary cause of this disorder.[4,5]

Cushing's disease (CD) results from overproduction of corticotropin by a pituitary adenoma, which in turn results in overproduction of cortisol from the adrenal cortex and a state of hypercortisolism. Other forms of CS are due to autonomous production of cortisol from adrenal cortical tumors, or ectopic corticotropin syndrome (overproduction of corticotropin from a nonpituitary tumor). CD and the ectopic corticotropin syndrome are often referred to as corticotropin-dependent CS, whereas adrenal cortical tumors cause corticotropin-independent CS. Approximately 75% to 90% of CS cases in children are due to CD. CD is uncommon in children under 6 years of age; adrenal causes of CS (adenoma, carcinoma, or bilateral hyperplasia) are the typical etiologic factors in younger children.

Autonomous secretion of cortisol from the adrenal glands, or corticotropin-independent CS, accounts for approximately 15% of all the cases of CS in childhood. CS is a manifestation of approximately one-third of all adrenal tumors. In adrenal cancer, adrenal adenomas, bilateral micronodular adrenal hyperplasia, and primary bilateral macronodular adrenocortical hyperplasia, a spectrum of tumor growth exists as a result of a variety of genetic defects that have been recently identified. (See discussion of the genetics of pituitary and adrenal tumors associated with CS, in this issue.)

The annual incidence of pediatric adrenocortical carcinoma (ACC) according to the Surveillance, Epidemiology, and End Results (SEER) database from 1973 through 2008 was 0.21 per million.[6] ACC has a bimodal age distribution, with a peak in early childhood at 3 years,[7] and a peak in adulthood in the 40s and 50s.[8] These tumors are characterized by poor survival, especially in the context of distant metastases, large tumor volume, and older age.[9] Adrenocortical cancers in childhood may be associated with the Li-Fraumeni or Beckwith-Wiedemann syndromes, and rarely with adenomatous polyposis coli and other rare genetic conditions.

Defects in cyclic adenosine monophosphate (cAMP) signaling underlie most cortisol-producing adrenal hyperplasia and tumors.[10] McCune Albright syndrome, in which a somatic mutation of the *GNAS1* gene leads to constitutive activation of the Gsa protein, may be associated with infantile CS.[11] Primary pigmented adrenocortical nodular disease (PPNAD) is a genetic disorder usually associated with Carney complex, a syndrome of multiple endocrine gland abnormalities in addition to myxomas and lentigines.[12] The adrenal glands in PPNAD are characterized by multiple pigmented nodules that autonomously secrete cortisol and are surrounded by an atrophic cortex. Children and adolescents with PPNAD frequently have periodic or cyclical CS. The underlying genetic defect in most forms of PPNAD is mutations of