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Annales d'Endocrinologie xxx (2017) xxx–xxx

Annales d'Endocrinologie
Annals of Endocrinology

Klotz Communications 2018: Cortisol and all its disorders

An update on Cushing syndrome in pediatrics

Devenir des complications du Cushing de l'enfant

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Abstract

Cushing syndrome (CS) in childhood results mostly from the exogenous administration of glucocorticoids; endogenous CS is a rare disease. The latter is the main reason pediatric patients with CS escape diagnosis for too long. Other barriers to optimal care of a pediatric patient with CS include improper following of the proper sequence of testing for diagnosing CS, which stems from lack of understanding of pathophysiology of the hypothalamic–pituitary–adrenal axis; lack of access to proper (i.e., experienced, state-of-the-art) surgical treatment; and unavailability of well-tolerated and effective medications to control hypercortisolemia. This report reviews the state-of-the-art in diagnosing CS and provides an update on the most recent discoveries in its genetics and treatment.

Keywords: Cushing syndrome; Pituitary tumors; Adrenal cortex; Carney complex; Adrenocortical hyperplasia; Adrenal cancer

Résumé

La plupart des syndromes de Cushing (SC) observés chez l'enfant sont associés à l'administration exogène de glucocorticoïdes ; les SC endogènes font partie des maladies rares, ce qui explique que chez l'enfant le SC échappe longtemps au diagnostic. D'autres obstacles au traitement approprié du SC s'expliquent par la nécessité d'un protocole d'examens adaptés à l'exploration de l'axe hypophyso-surrénalien permettant l'identification de l'origine du SC chez l'enfant ; l'accessibilité de la chirurgie hypophysaire qui nécessite une équipe expérimentée; et l'absence de traitement bien toléré et efficace pour le contrôle de l'hypercorticisme. Dans cette revue, l'état des connaissances actuelles pour le diagnostic du SC et les découvertes récentes en termes de génétique et de thérapeutique seront présentés.

Mots clés : Syndrome de Cushing ; Tumeurs de l'hypophyse ; Cortex surrénal ; Complexe de Carney ; Hyperplasie corticosurrénalien ; Cancer des glandes surrénales

1. Introduction

Corticotropin (ACTH)-releasing hormone (CRH) is synthesized in the hypothalamus and carried to the anterior pituitary in the portal system. CRH stimulates Adrenocorticotropic hormone (ACTH) release from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol (hypothalamic–pituitary–adrenal or HPA axis) [1,2]. Cortisol inhibits the secretion of primarily CRH and secondarily ACTH in a negative feedback regulation system. In Cushing syndrome (CS), the HPA axis has lost its ability for self-regulation, due to excessive secretion of either ACTH 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 Cushing syndrome to guide therapy toward the primary cause of this disorder [3,4].

2. Epidemiology and etiology

Endogenous CS is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol. The overall incidence of endogenous CS is 0.7–2.4 per million people per year [5]. Only approximately 10% of the new cases each year occur in children. In both adults and children, CS is most

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https://doi.org/10.1016/j.ando.2018.03.010
0003-4266/

commonly caused by an ACTH-secreting pituitary tumor. Under normal conditions, cortisol is secreted from the cortical cells of the adrenal glands under the control of the pituitary hormone ACTH (adrenocorticotropic hormone). Cushing disease (CD) results from overproduction of ACTH 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 and the ectopic ACTH syndrome which is due to overproduction of ACTH from a non-pituitary tumor. CD and the ectopic ACTH syndrome are often referred to as ACTH-dependent CS whereas adrenal cortical tumors cause ACTH-independent CS. The etiology of CS is most commonly Cushing disease (CD) in both adults and children; about 10% of all CS cases occur in children. Approximately 75–90% of CS cases in children are due to CD.

CD is very uncommon in children under 6 years of age; adrenal causes of CS (adenoma, carcinoma, or bilateral hyperplasia) are the typical etiologies in younger children. CS caused by increased production of cortisol from one of the body's tissues, whether due to an ACTH-dependent or ACTH-independent cause, is often called "endogenous" CS. 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.

Autonomous secretion of cortisol from the adrenal glands, or ACTH-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. Details surrounding the genetics of pituitary and adrenal tumors associated with CS are discussed in a separate chapter.

The annual incidence of pediatric adrenocortical carcinoma according to the SEER database from 1973 through 2008 was 0.21 per million [6]. Adrenocortical carcinoma 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 cAMP signaling underlie the majority of 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 the *PRKAR1A* gene coding for the regulatory type I-alpha (RIalpha) subunit of protein kinase A (PKA) [13].

Ectopic ACTH production occurs rarely in young children, and accounts for less than 1% of the cases of CS in adolescents [14]. Sources of ectopic ACTH include carcinoid tumors in the bronchus, pancreas, or thymus; medullary carcinomas of the thyroid, small cell carcinoma of the lung, pheochromocytomas; and other pancreatic and gastrointestinal neuroendocrine tumors. Ectopic ACTH/CRH co-secreting tumors are also extremely rare in children and adolescents. The diagnosis of this condition is frequently missed and is sometimes confused with CD due to the effect of CRH on the pituitary [15].

3. Clinical presentation

In most children, the onset of CS is insidious [1–3,16]. The most common presenting symptom is weight gain; in childhood, lack of height gain concomitant with weight gain is the most common presentation of CS. Other common problems reported in children include facial plethora, headaches, hypertension, hirsutism, glucose intolerance, kidney stones, fractures, amenorrhea, and delayed sexual development [17–20]. Pubertal children may present with virilization. Skin manifestations, including acne, violaceous striae, bruising, fungal infections, acanthosis nigricans, and supra-temporal and supra-clavicular fat pads, are also common [1,16]. Compared with adult patients with CS, symptoms that are less commonly seen in children include sleep disruption, muscular weakness and/or myopathy, and problems with memory. Skin striae (stretchmarks) are also almost never present before the age of 5–7 years of age.

4. Diagnostic guidelines

Accurate diagnosis and classification of CS is crucial for determining the appropriate therapeutic intervention. The clinical evaluation and medical history, especially review of growth data, are important to make the initial diagnosis. Upon suspicion of CS, laboratory and imaging confirmations are necessary. An algorithm of the diagnostic process is presented in Fig. 1. The Endocrine Society published guidelines on the diagnostic workup of CS in 2008 [4].

The first step in the diagnosis of CS is documentation of hypercortisolism. This can be done with the 24-urinary free cortisol (UFC) with at least 2, preferably 3 consecutive collections, corrected for body surface area; late-night salivary cortisol; and/or a low-dose dexamethasone-suppression test (DST; 1 mg overnight or 2 mg/day over 48 hours). None of these tests has 100% diagnostic accuracy; each test has its own limitations, and multiple tests are usually needed to establish the diagnosis. In some studies, late-night salivary cortisol has been shown to have superior diagnostic performance to UFC, and it has been shown to be a simple, accurate way to screen for hypercortisolism in children [21–23], however there is much variation in laboratory performance of this test. Recently, hair cortisol

Please cite this article in press as: Stratakis CA. An update on Cushing syndrome in pediatrics. Ann Endocrinol (Paris) (2017), https://doi.org/10.1016/j.ando.2018.03.010