Neonatal Cushing Syndrome

A Rare but Potentially Devastating Disease

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KEYWORDS

• Cushing syndrome • Hypercortisolemia • Adrenocortical tumors
• Adrenal hyperplasia • Infant

KEY POINTS

- Neonatal Cushing syndrome (CS) is a rare disorder, but it can lead to significant complications and even death, if not diagnosed and treated promptly.
- Adrenocortical tumors (ACTs) are a common cause of neonatal CS and they can be adrenocortical carcinomas.
- Neonatal CS may present as part of a genetic syndrome, such as Li-Fraumeni syndrome, McCune-Albright syndrome, Beckwith-Wiedemann syndrome, and DICER1 mutations.
- Diagnosis includes documentation of loss of the circadian rhythm of cortisol production (after it has been established), elevation of urinary free cortisol, and lack of suppression of cortisol production after dexamethasone administration.
- Surgical resection of the adrenal tumor is the current approach of treatment for ACTs. Adjuvant chemotherapy should be considered in cases of adrenocortical carcinomas.

INTRODUCTION

Cushing syndrome (CS) is named after Dr Harvey Cushing, an American neurosurgeon who first described the condition in a patient with weight gain, round face, hypertrichosis, muscle weakness, and irregular menstruations in 1912.[1] The term CS is currently

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used to describe the constellation of signs and symptoms that result from the chronic effects of hypercortisolemia.[2]

The etiology of CS is divided into exogenous (or iatrogenic) CS and endogenous (adrenocorticotropic hormone [ACTH]-dependent and ACTH-independent) CS. The widespread use of glucocorticoid (GC) treatment for various conditions (autoimmune, malignant, allergic) has rendered exogenous CS a common condition.[3,4] The endogenous type is much more rare, with an estimated incidence of 2 to 5 new cases per million people diagnosed every year; of these, only 10% refer to children. Endogenous neonatal CS is extremely rare. Most of the cases present as part of an isolated adrenocortical tumor (ACT), often an adrenocortical carcinoma. Nearly 100 patients with neonatal and infantile CS not associated with isolated ACTs have been described to date (Supplemental Table 1).[5]

CS is associated with significant clinical findings, such as hypertension, hyperglycemia, hyperlipidemia, decreased bone mineral density, and muscular atrophy. More characteristically in children, CS also leads to growth arrest, despite continuous weight gain.[5] Given the severity of the various comorbidities, which may result in long-term and irreversible complications, it is essential to recognize and appropriately manage CS as soon as possible in any age, but particularly in infancy.

THE FETAL AND NEONATAL HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The adrenal glands derive from the urogenital ridge of the intermediate mesoderm, which also differentiates into the gonads and the mesonephros.[6,7] The development of the steroid-producing cells starts at 4 weeks of gestation, and at 5 weeks the adrenal cells are clearly separated from the gonads.[8] Around the same period (7 weeks of gestation), sympathetic nerve cells from the neural crest migrate to the center of the adrenals to form the adrenal medulla.[6] At 8 weeks of gestation, adrenals are distinct organs and the adrenal cortex consists of 2 separate zones, the fetal and the definitive zone.[9,10]

The fetal zone comprises almost 80% of the adrenal gland volume at term and it is a hormonally active region. However, it has low levels of 3-beta hydroxysteroid dehydrogenase and high levels of sulfotransferase enzyme concentrations, which renders dehydroepiandrosterone and dehydroepiandrosterone sulfate (DHEAS) the main product of the fetal zone.[11] Those substances are further used by the placenta to maintain the estriol levels.[12]

The fetal zone starts to involute after birth and disappears by the end of the first year of life.[10] The definitive zone, the outer zone that surrounds the fetal cortex, increases in size with age and it gives rise to the 3 known zones of the adult adrenal cortex (glomerulosa, fasciculata, and reticularis) within the first 1 to 3 years of life; development of zone reticularis is not completed until the puberty years.[13]

Cortisol has been detected as early as 8 weeks of gestation, and it has significant functions during the intrauterine life, including for the maturation of lungs, liver, thyroid, and other organs.[14] The human fetal adrenal gland starts also secreting aldosterone, desoxycorticosterone, and corticosterone between 10 and 20 weeks.[10] As mentioned, DHEAS levels are high at birth but decrease rapidly afterward as the fetal zone involutes.[10]

The adrenal production of cortisol is under the control of the HPA axis. Corticotropin-releasing hormone (CRH) production has been reported in primates by the third trimester.[15] However, sources of CRH production outside the hypothalamus, such as the placenta, have also been documented to contribute significantly in the cortisol production during embryogenesis.[16] The anterior lobe of the pituitary, where ACTH hormone is produced, derives from the oral ectoderm and it is fully formed by 5 weeks of gestation. Although ACTH is detected in the fetal pituitary by