Congenital Adrenal Hyperplasia: An Endocrine Disorder with Neonatal Onset

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KEYWORDS

• Neonatal • Endocrine • Adrenal • Ambiguous genitalia
• Metabolic disorder • Salt-loss • Newborn • Genetic disorder

Our understanding of endocrine disorders in the neonate has increased in the wake of considerable advances in the fields of genetics and cell biology. In newborn nurseries and neonatal intensive care units (NICUs), endocrine dysfunction is encountered less often than disease of the respiratory, cardiac, or gastrointestinal system; in fact, we rarely think of it except when reviewing the results of a newborn metabolic screen. Endocrine dysfunction is deserving of our attention, however, because of the potentially grave consequences of unrecognized disease in the neonate. One acute clinical endocrine disorder manifesting shortly after birth is congenital adrenal hyperplasia (CAH), the most common cause of ambiguous genitalia in the newborn and, at times, the cause of sudden neonatal death. The management of a newborn with ambiguous genitalia has changed in recent years, and it is essential for caregivers to review the latest recommendations. The first part of this article reviews the pathophysiology and management of CAH, and the second deals with issues related to ambiguous genitalia in the CAH-affected child. To grasp the pathophysiology of CAH, a fundamental understanding of the endocrine system is required.

THE ENDOCRINE SYSTEM

The classic endocrine system encompasses a diverse group of ductless secretory glands: the hypothalamus, pineal, pituitary, thyroid, parathyroid, thymus, pancreatic islet cells, adrenals, ovaries, and testes. Among the wide-ranging responsibilities of the endocrine system are coordination and regulation of metabolism, growth and development, and reproduction. The endocrine and central nervous systems are intimately linked, forming the neuroendocrine system, which has the complex task of controlling body homeostasis.

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Endocrine glands and tissues throughout the body synthesize, store, and secrete hormones, the chemical messengers of the neuroendocrine system. After secretion into the blood or extracellular fluid, hormones exert their actions on specific target cells located in nearby or distant tissues. Target cells contain specific receptors to which corresponding hormones must attach to exert physiologic actions.

Hormones are powerful negative feedback regulators of their own production. As hormones reach target levels, the anterior pituitary and hypothalamus are suppressed, ceasing production of the respective trophic and releasing hormones. Endocrine disease can be associated with hormone overproduction, hormone underproduction, or altered tissue responses to hormones.[1] The endocrine disorder CAH involves a failure to produce the hormones cortisol and aldosterone, along with inappropriate production of androgens.

Adrenal Hormones

The adrenal glands are located at the superior poles of the kidneys. Each gland is composed of two distinct independently functioning organs: the inner medulla, which produces catecholamines, and the outer cortex, which synthesizes three classes of steroid hormones (mineralocorticoids, glucocorticoids, and androgens). Adrenal steroid production and regulation require a functional hypothalamic-pituitary-adrenal (HPA) axis.

The release of cortisol, the body's major glucocorticoid, is controlled by regulating its rate of synthesis. Central nervous stimulation, such as that associated with stress, surgery, extreme heat or cold, hypoxia, infection, hypoglycemia, or injury, prompts the release of corticotropin-releasing factor (CRF) from the hypothalamus. CRF binds to receptors in the anterior pituitary, where it stimulates the release of corticotropin into the bloodstream. In the adrenal cortex, corticotropin stimulates the synthesis and release of cortisol. The increasing circulating cortisol level exerts negative feedback stimulation on the hypothalamus and anterior pituitary to suppress CRF and corticotropin, respectively, thereby inhibiting further production of cortisol. This regulatory system is known as a closed negative feedback loop (**Fig. 1**).

Aldosterone, the chief mineralocorticoid, regulates the renal retention of sodium and water and the excretion of potassium. Aldosterone is critical to electrolyte balance, blood pressure, and intravascular volume and is itself regulated by the plasma renin-angiotensin (PRA) system. Renin, released by the kidneys, stimulates the formation of angiotensin, a powerful vasoconstrictor that, in turn, stimulates the release of aldosterone from the adrenal cortex.

The adrenal androgens (dehydroepiandrosterone [DHEA], DHEA sulfate, and androstenedione) are regulated by corticotropin. These steroids have minimal androgenic activity on their own but are converted in the peripheral tissues to two more potent androgens, testosterone and dihydrotestosterone (DHT). These latter hormones are largely responsible for virilization of the external genitalia in the male fetus.

CONGENITAL ADRENAL HYPERPLASIA

CAH is a deficiency in one of five enzymes required to synthesize cortisol from cholesterol in the adrenal cortex. Mutations in the 21-hydroxylase (21-OHD) gene, of which there are more than 50, are, by a large margin, the most frequent cause of CAH.[2] The 21-OHD form of CAH accounts for 95% of cases and is the chief cause of ambiguous genitalia in the neonate. Of the remaining four relatively rare enzyme deficiencies, 11β-hydroxylase deficiency is most frequent. A recently described type of CAH is P450