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PEDIATRIC ENDOCRINOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Pediatric Endocrinology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in pediatric endocrinology. Each manual reviews a topic essential to the current practice of pediatric endocrinology.

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Adrenal Insufficiency in Childhood

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Adrenal Insufficiency in Childhood

Ellen E. Kim, MD, and Jill D. Jacobson, MD

INTRODUCTION

Adrenal insufficiency refers to a group of disorders characterized by abnormally diminished secretion of hormones from the adrenal gland. Clinically, the term is most often used to describe deficiency of hormones produced in the adrenal cortex. Adrenal insufficiency may be *primary* (the result of disorders intrinsic to the adrenal cortex), or it may be *secondary* or *tertiary* (the result of disorders involving the pituitary or hypothalamic regulation of the adrenal glands, respectively). Secondary and tertiary forms of adrenal insufficiency are also referred to as *central* adrenal insufficiency.

Signs and symptoms of adrenal insufficiency can be nonspecific, making the diagnosis difficult. Identifying adrenal insufficiency is important, as it is a life-threatening condition. Correctly determining the status of the hypothalamic-pituitary-adrenal (HPA) axis is crucial to allow prompt institution of replacement therapy and prevent unnecessarily committing a patient to long-term glucocorticoid treatment.

ADRENAL STRUCTURE AND FUNCTION

ANATOMY

The adrenal glands are paired structures named for their anatomic location next to the kidneys. Each gland consists of a capsule, cortex, and medulla. Although the cortex and medulla are in close proximity, they are typically regarded as distinct organs. The cortex constitutes 80% to 90% of the adrenal gland and forms the outer zone of the gland; it is the source of steroid hormones. The adrenal cortex has 3 discrete regions: the glomerulosa (outer zone), fasciculata (middle zone), and reticularis (inner zone). The medulla, the tiny inner zone of the adrenal gland, is the source of catecholamines (epinephrine, norepinephrine, dopamine). Embryologically, the cortex and medulla have different origins. By postconception day 25, the fetal adrenal cortex begins to form from cells of mesodermal origin, whereas the fetal adrenal medulla arises from neural crest cells that migrate to the center of the gland after 8 weeks postconception.[1]

Each adrenal gland is supplied by the superior, middle, and inferior suprarenal arteries, which arise directly or indirectly from the abdominal aorta. The arteries anastomose over the gland surface and descend inwardly from the capsule. Steroid hormone concentrations increase gradually from the outer to the inner cortex. Because of the redundant blood supply, hemorrhage and thromboembolic insults to the adrenal gland generally cause only transient adrenal insufficiency. These vascular events are usually reversed by compensatory hyperplasia of the unaffected portions of the gland.

STEROIDOGENESIS

The adrenal cortex produces glucocorticoids, mineralocorticoids, and sex steroids. Cortisol is the most important glucocorticoid, and aldosterone is the most potent mineralocorticoid. Dehydroepiandrosterone (DHEA) is the major androgenic precursor produced in the adrenal cortex.

Pathways

Initiation of adrenal steroid biosynthesis occurs by passive transfer and active transport of cholesterol into the adrenal cells (**Figure**). Cholesterol is converted to a precursor steroid, pregnenolone, which is subsequently converted to the individual adrenal steroid hormones by a series of biochemical events in the 3 main regions of the cortex. The specific enzymes present in the cells in each zone dictate the exact steroid hormone produced. For example, the zona glomerulosa, the site of mineralocorticoid production, is unique in expressing aldosterone synthase, which is essential for catalyzing the 3 final steps of aldosterone production. The zona fasciculata is the main site of synthesis of glucocorticoids, which include cortisol and other intermediates that possess more modest glucocorticoid activity. The adrenal sex steroids are primarily produced in the zona reticularis, although the zona fasciculata also contributes to their production; the key enzyme in their production is 17α-hydroxylase.

Regulation

Production of glucocorticoids and adrenal androgens is under the control of the HPA axis. Neurons in the paraventricular nucleus of the hypothalamus

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