Adrenal Insufficiency in Childhood

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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.

STERIDOGENESIS

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
synthesize corticotropin-releasing hormone (CRH), which reaches the pituitary portal circulation and stimulates adrenocorticotropic hormone (ACTH) synthesis and release from the anterior pituitary. ACTH, which is a fragment of the pro-opiomelanocortin (POMC) molecule, then stimulates steroidogenesis in the adrenal cortex. Both CRH and ACTH are G protein–coupled hormones that act via adenylate cyclase and intracellular cyclic adenosine monophosphate. Cortisol is the main regulator of HPA axis activity by its negative-feedback effects on both ACTH and CRH.

Aldosterone secretion is regulated by the renin-angiotensin system rather than by CRH and ACTH. The renal juxtaglomerular apparatus senses decreases in volume status and causes an increase in renin, an enzyme that cleaves angiotensin-converting enzyme (ACE) to angiotensin I, which is further activated by ACE to angiotensin II in the lung and other sites. Angiotensin II potently stimulates aldosterone secretion.

**MAJOR FUNCTIONS AND EFFECTS OF ADRENAL STEROIDS**

**Glucocorticoids**

The term glucocorticoid refers to the glucose-regulating properties of these hormones. Their primary effect on carbohydrate metabolism is to increase hepatic gluconeogenesis. Glucocorticoids exert insulin antagonistic properties in tissues other than the liver and increase cellular resistance to insulin in most tissues. They increase lipolysis and exert a catabolic effect on protein metabolism.

Glucocorticoids also play a major role in free water excretion and vascular tone. They regulate free water clearance by increasing renal blood flow and glomerular filtration rate (GFR). Glucocorticoid deficiency leads to decreased GFR. This is the mechanism by which glucocorticoid deficiency can mask diabetes insipidus.

Glucocorticoids exert potent effects on the immune system by several mechanisms. All major leukocyte populations bear glucocorticoid receptors. Glucocorticoids alter trafficking of all leukocyte populations, inhibiting recruitment of neutrophils and macrophages to inflammatory sites. Glucocorticoids exert a greater effect on T-cell immunity than on humoral immunity. The immunosuppressive effects play a major role in the toxicities seen with glucocorticoid excess. Infections are a major cause of morbidity and mortality in both endogenous and exogenous glucocorticoid excess.

Glucocorticoids cross the blood-brain barrier and exert direct effects on the brain. The effects on mood and behavior are well recognized. Excessive glucocorticoids can cause insomnia, irritability, and emotional lability. Long-term excessive glucocorticoid exposure leads to cerebral atrophy and cognitive decline in children. Excessive glucocorticoids also inhibit growth hormone (GH) secretion and exert a direct inhibitory effect on the growth plates, leading to decreased linear growth and skeletal maturation in children.

**Mineralocorticoids**

The major function of aldosterone is to maintain the intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. The renal collecting tubules are the major site of action of the
A d r e n a l  I n s u f f i c i e n c y  i n  C h i l d h o o d

Mineralocorticoids. Although aldosterone is by far the most potent endogenous mineralocorticoid, other steroids, including 11-deoxycorticosterone (DOC) and cortisol, exert mineralocorticoid activity. Aldosterone is about 400 times more potent as a mineralocorticoid than cortisol.

Mineralocorticoid deficiency is usually associated with primary adrenal insufficiency. Pseudohypaldosteronism is a rare cause of mineralocorticoid deficiency characterized by target organ unresponsiveness to the action of aldosterone.

Table 1. Causes of Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Primary Adrenal Insufficiency</th>
<th>Infection/infiltration</th>
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<tbody>
<tr>
<td>Autoimmune adrenal disease</td>
<td>Tuberculosis</td>
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<td>Isolated adrenal insufficiency (Addison’s disease)</td>
<td>Amyloidosis</td>
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<td>Autoimmune polyglandular syndromes</td>
<td>Hemochromatosis</td>
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<td>Inborn error of metabolism</td>
<td>Sarcoïdosis</td>
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<td>Congenital adrenal hyperplasia</td>
<td>HIV/AIDS</td>
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<td>StAR deficiency</td>
<td>Histoplasmosis</td>
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<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Blastoïcosis</td>
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<td>X-linked adenoleukodystrophy</td>
<td>Cryptococcosis</td>
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<tr>
<td>DAX-1 mutation</td>
<td>Cocciïdoidomycosis</td>
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<tr>
<td>Familial glucocorticoid deficiency</td>
<td>Drugs</td>
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<tr>
<td>Wolman’s disease</td>
<td>Aminogluthéïtidime</td>
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<tr>
<td>SF-1 mutation</td>
<td>Etomidade</td>
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<tr>
<td>Adrenal hemorrhage</td>
<td>Ketoconazol</td>
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<tr>
<td>Birth trauma</td>
<td>Metyrapone</td>
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<tr>
<td>Sepsis (Waterhouse-Friderichen syndrome)</td>
<td>Suramin hexasodium</td>
</tr>
<tr>
<td>Shock</td>
<td>Phénytoïn</td>
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<tr>
<td>Coagulopathies</td>
<td>Barbiturates</td>
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<tr>
<td>Ischemia</td>
<td>Rifampin</td>
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<td>Miotane</td>
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<tr>
<th>Secondary Adrenal Insufficiency</th>
<th>Pituitary developmental abnormalities</th>
</tr>
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<tbody>
<tr>
<td>Central nervous system lesions</td>
<td>Septo-optic dysplasia</td>
</tr>
<tr>
<td>Hypothalamic/pituitary/suprasellar tumor</td>
<td>Hydranencephaly/ anencephaly</td>
</tr>
<tr>
<td>Trauma/hemorrhage</td>
<td>Pituitary aplasia/hypoplasia</td>
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<tr>
<td>Sarcoïdosis, tuberculosis, fungal infection</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Empty sella syndrome</td>
<td>Supraphysiologic glucocorticoid administration</td>
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<tr>
<td>CRH deficiency</td>
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<tr>
<td>POMC deficiency</td>
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CRH = corticotropin-releasing hormone; DAX-1 = dose-sensitive sex-reversal adrenal hypoplasia congenita; POMC = pro-opiomelanocortin; SF-1 = steroidogenic factor; StAR = steroidogenic acute regulatory protein. (Adapted with permission from Bethin KE, Muglia LJ. Adrenal insufficiency. In: Radovick S, MacGillivray MH, editors. Pediatric endocrinology: a practical guide. Totowa [NJ]: Humana Press; 2003:208.)

Sex Steroids

DHEA has no intrinsic androgenic activity, but it can be converted in the peripheral tissues and in the adrenal gland to the androgens androstenedione and testosterone. DHEA is metabolized by sulfation to form DHEA sulfate (DHEAS). In contrast to other steroids, the sulfated steroids such as DHEAS bind with high affinity to albumin. Slower clearance of sulfated steroids results in longer half-lives. Although the adrenal glands are a major source of androgens in females, they are a minor source of androgens in postpubertal males.

CAUSES AND CLINICAL FEATURES OF ADRENAL INSUFFICIENCY

Primary and central (secondary or tertiary) adrenal insufficiency can lead to widely differing clinical features. Knowledge of these differences will aid in quickly determining the proper diagnosis, thus allowing the identification of other associated conditions.

PRIMARY CAUSES

Primary adrenal insufficiency is defined as an intrinsic abnormality of the adrenal gland involving impaired adrenal steroidogenesis, adrenal dysgenesis, or adrenal destruction. Table 1 lists the range of primary causes.

Congenital Adrenal Hyperplasia

Although tuberculosis remains the most common cause of primary adrenal insufficiency worldwide, congenital adrenal hyperplasia (CAH) is the most common cause in children from developed countries, with worldwide incidence estimated to be 1 in 8000 to 14,000 live births. CAH also is the leading cause of genital ambiguity. CAH is caused by abnormal steroidogenesis that may arise from inherited deficiency of any of 6 enzymatic steps involved in the conversion of cholesterol to cortisol (Table 2).

In 95% of cases, CAH is caused by deficiency of 21-hydroxylase (resulting from a mutation in the CYP21A2 gene). The underlying defect in these cases is insufficient production of cortisol and lack of central feedback leading to increased CRH and ACTH secretion. The adrenal glands then become hyperplastic. There is an accumulation of sex steroid precursor hormones that do not require 21-hydroxylation. The excess sex steroid precursors are converted to potent androgens (testosterone and dihydrotestosterone), resulting in antenatal virilization of females. Males do not display genital ambiguity. Thus, the term “adrenogenital syndrome”
### Table 2. Potential Causative Defects in CAH: Clinical Features, Laboratory Findings, and Approach to Therapy

<table>
<thead>
<tr>
<th>Defect</th>
<th>Signs and Symptoms</th>
<th>Laboratory Findings</th>
<th>Therapy</th>
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<tr>
<td><strong>21-hydroxylase deficiency</strong></td>
<td><strong>Classic form:</strong> Salt-wasting crisis and genital ambiguity in females and prenatals</td>
<td><strong>↑ Baseline and ACTH-stimulated 17-OHP</strong> and <strong>↓ Androgens</strong>; <strong>↑ Renin, ↓ Na, ↑ K</strong></td>
<td>Glucocorticoid and mineralocorticoid replacement; Salt supplementation</td>
</tr>
<tr>
<td></td>
<td><strong>Nonclassic form:</strong> Premature pubarche and disordered pubertal patterns</td>
<td><strong>↑ Baseline and ACTH-stimulated 17-OHP</strong> and <strong>↑ Androgens</strong>; <strong>↑ Renin</strong></td>
<td>Glucocorticoid administration; Mineralocorticoid replacement if renin is elevated</td>
</tr>
<tr>
<td><strong>11β-hydroxylase deficiency</strong></td>
<td>Genital ambiguity in females and hypertension</td>
<td><strong>↑ Baseline and ACTH-stimulated compound S and DOC</strong> and <strong>↓ Androgens</strong>; <strong>↑ Renin, ↑ Na, ↓ K</strong></td>
<td>Glucocorticoid administration; Salt supplementation</td>
</tr>
<tr>
<td><strong>3β-HSD deficiency</strong></td>
<td>Salt-wasting crisis and genital ambiguity in males and females; Premature pubarche</td>
<td><strong>↑ Baseline and ACTH-stimulated Δ5 steroids (17-OH-pregnenolone, DHEA)</strong>; <strong>↑ Δ5/Δ4 steroids</strong>; <strong>↑ Renin, ↓ Na, ↑ K</strong></td>
<td>Glucocorticoid and mineralocorticoid administration</td>
</tr>
<tr>
<td><strong>17α-hydroxylase deficiency</strong></td>
<td>Genital ambiguity in males and hypertension</td>
<td><strong>↑ DOC, corticosterone</strong> and <strong>Low 17α-hydroxylated steroids and poor response to ACTH</strong>; <strong>↓ Renin, ↑ Na, ↓ K</strong></td>
<td>Glucocorticoid administration; Sex hormone replacement</td>
</tr>
<tr>
<td><strong>Cholesterol desmolase deficiency</strong></td>
<td>Salt-wasting crisis and genital ambiguity in males</td>
<td><strong>Low levels of all steroid hormones</strong> and <strong>Decreased/absent response to ACTH</strong>; <strong>↑ Renin, ↓ Na, ↑ K</strong></td>
<td>Glucocorticoid and mineralocorticoid administration; Salt supplementation</td>
</tr>
<tr>
<td><strong>Cytochrome P450 oxioreductase deficiency</strong></td>
<td>Wide variability in affected phenotype; Premature virilization without progressive postnatal virilization in females</td>
<td><strong>↑ Ratio of pregnenolone and progesterone to cortisol</strong> and <strong>↑ Urinary excretion of pregnenolone, pregnane-triolone, pregnenediol, and pregnanediol during pregnancy</strong></td>
<td>May require glucocorticoid administration</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; CAH = congenital adrenal hyperplasia; DHEA = dehydroepiandrosterone; DOC = 11-deoxycorticosterone; 3β-HSD = 3β-hydroxysteroid dehydrogenase; 17-OH-pregnenolone = 17 α-hydroxypregnenolone; 17-OHP = 17α-hydroxyprogesterone. (Adapted with permission from Levine LS, Oberfield SE. Congenital adrenal hyperplasia. In: Radovick S, MacGillivray MH, editors. Pediatric endocrinology: a practical guide. Totowa [NJ]: Humana Press; 2003:230–1.)

is now considered a misnomer. Historically, patients with 21-hydroxylase deficiency have been classified as having “salt-wasting” or “non—salt-wasting” disease. Such distinctions are somewhat artificial, as these patients manifest a spectrum of severity of mineralocorticoid deficiency. Even patients with no detectable electrolyte or blood pressure abnormalities may have subclinical mineralocorticoid deficiency. Approximately 75% of patients with 21-hydroxylase deficiency display elevated renin levels, making renin measurement an excellent screening tool to identify subclinical mineralocorticoid deficiency. CAH secondary to 21-hydroxylase deficiency has also been classified historically as “classic” (severe) and “nonclassic” (mild). Again, these distinctions are somewhat artificial, as there is a spectrum of disease severity. Male infants with salt-wasting and female infants with ambiguous genitalia are described as having classic CAH. Patients with nonclassic CAH can present later in childhood and do not have salt-wasting as a prominent feature. Nonclassic CAH caused by 21-hydroxylase deficiency can present as premature pubarche in childhood and in pubertal females can cause irregular menses, hirsutism, acne, and infertility.

Approximately 5% of cases of CAH are caused by 11β-hydroxylase deficiency (resulting from a CYP11B1 mutation). Cortisol production is insufficient and androgens are produced in excess. As in 21-hydroxylase deficiency, affected females can present with ambiguous genitalia at birth, whereas males display no genital ambiguity. In contrast to 21-hydroxylase deficiency, 11β-hydroxylase deficiency also is associated with excessive production of DOC, an aldosterone precursor that possesses...
mineralocorticoid activity. This enzymatic defect can result in hypertension, hypernatremia, and hypokalemia.

An uncommon cause of CAH is 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency (HSD3B2 mutation). Because 3β-HSD is involved in an earlier step in the adrenal steroid pathway, synthesis of all steroid hormones can be affected. Resultant deficiencies of glucocorticoids and mineralocorticoids can lead to hypoglycemia, salt-wasting, and hypovolemia in affected neonates. 3β-HSD deficiency is associated with an accumulation of weak adrenal androgens along with a deficiency of potent androgens. The clinical implication of this is that females can be overvirilized, whereas males tend to be undervirilized. A mild, or “nonclassic,” form of CAH resulting from 3β-HSD deficiency was once thought to occur commonly in women with hyperandrogenism, hirsutism, and infertility. However, with the cloning of HSD3B2, mutations in the gene are now known to be extremely rare. Some patients with idiopathic hirsutism and infertility display hormonal profiles indistinguishable from those seen in 3β-HSD deficiency. The etiology of these hormonal abnormalities remains to be determined.6

Lipoid CAH is a rare, severe form of CAH caused by a deficiency of cholesterol desmolase (CYP11A mutation). Because conversion of cholesterol to pregnenolone is affected, there is decreased production of all adrenal steroids. Neonates can present with adrenal crisis, and male infants have female genitalia as a result of deficient androgen production.

Combined 17α-hydroxylase/17,20 lyase deficiency (CYP17 mutation) causes shunting of cortisol precursors to the mineralocorticoid pathway, resulting in excess DOC, which can lead to hypertension, hypernatremia, and hypokalemia. Concomitant deficiency of androgens results in undervirilization in the male.

Cytochrome P450 oxidoreductase deficiency is a relatively newly described, rare cause of CAH involving a mutation that affects electron transfer to CYP21A2 and CYP17.9 Affected girls have ambiguous genitalia, but virilization does not progress after birth. Androgen levels are low or normal. Conversely, affected boys can be undermasculinized. Bone malformations typical of Antley-Bixler syndrome can also be seen.

Other Primary Causes

Autoimmune adrenal failure. The second most common cause of primary adrenal insufficiency is autoimmune adrenal insufficiency, also known as Addison’s disease.6 Adrenal antibodies can be detectable in up to 86% of patients, depending on the assay.10 Autoimmune adrenal insufficiency can occur as an isolated condition or in association with other endocrinopathies as part of autoimmune polyglandular syndrome (APS) type 1 or APS type 2. Approximately 70% of cases of primary adrenal insufficiency in industrialized nations are associated with the polyglandular autoimmune disorders.11 Characteristic features of these 2 disorders are compared in Table 3.

APS type 1 (also known as APECED, or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy) is caused by a mutation in the gene that codes for an autoimmune regulatory protein involved in peripheral immune tolerance (AIRE gene); it typically presents in early childhood as chronic mucocutaneous candidiasis, acquired hypoparathyroidism, and adrenal failure.12 Other associated autoimmune endocrinopathies include (in decreasing order of frequency): hypogonadism, alopecia areata, vitiligo, autoimmune hepatitis, pernicious anemia, and type 1 diabetes.13 APS type 2 occurs more commonly than APS type 1 and typically presents in the third to fourth decade of life. Features of APS type 2 include primary adrenal failure, autoimmune thyroiditis, and type 1 diabetes. Other associated endocrinopathies can include autoimmune gastritis, pernicious anemia, and

| Table 3. Characteristic Features of the Autoimmune Polyglandular Syndromes |
|-----------------------------|-----------------------------|
| APS 1 | APS 2 |
| **Frequency** | **Onset** | **Genetics** | **Hereditary** | **Gender** | **Frequency** | **Onset** | **Frequency** | **Onset** |
| Less common | Infancy/childhood | AIRE gene, chromosome 21 | Autosomal recessive | M = F | 30%–60% | Infancy/childhood | HLA-DR/DQ- associated | Polygenic |
| More common | Late childhood/ adulthood | None | None | Female predominance | 3.5%–10% | Childhood | None |
| **Hypparathyroidism** | 77%–89% | 4%–18% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 70%–100% | 7%–17% | 5% |
| **Mucocutaneous candidiasis** | 73%–100% | 8%–40% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 70%–100% | 4%–13% | 4%–5% |
| **Ectodermal dysplasia** | 77% | 12%–15% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Addison’s disease** | 60%–86% | 8%–40% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Type 1 diabetes mellitus** | 4%–18% | 12%–15% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Autoimmune thyroiditis** | 70% | 2%–25% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Pernicious anemia** | 70%–100% | 2%–25% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Gonadal failure** | 7%–17% | 7%–17% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Female** | 3.5%–10% | 5% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Male** | 7%–17% | 5% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Vitiligo** | 4%–5% | 7%–17% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Alopecia** | 4%–13% | 7%–17% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Autoimmune hepatitis** | 2% | 7%–17% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |
| **Malabsorption** | 2% | 7%–17% | 3β-Hydroxysteroid dehydrogenase (3β-HSD) | 3β-HSD deficiency (HSD3B2 mutation) | 2%–25% | 10%–18% | Rare |

AIRE = autoimmune regulator; HLA = human leukocyte antigen.
Secondary and tertiary causes are associated with abnormalities of the hypothalamus and result in ACTH and CRH deficiencies, respectively, and related to adrenal hemorrhage. Antibody syndrome are at risk for adrenal insufficiency and fungal infections. Patients with antiphospholipid syndrome, are at risk for adrenal insufficiency. The natural history of the adrenal hemorrhage of the adrenal glands, with resultant adrenal insufficiency. Other causes of adrenal insufficiency may present with decreased axillary and pubic hair. Adrenal androgen deficiency in pubertal males may not be clinically apparent, as testicular androgen production may be sufficient to drive axillary and pubic hair growth.
pubic hair development. Prepubertal children are largely asymptomatic from an androgen standpoint.

A sign suggestive of primary adrenal insufficiency is hyperpigmentation. The hyperpigmentation occurs in sun-exposed areas and is the result of increased production of POMC (the peptide precursor for ACTH) in response to the cortisol deficiency, the cleavage products of which include melanocyte-stimulating hormone.

Central (secondary or tertiary) adrenal insufficiency has a more chronic or indolent presentation. Like patients with primary disease, patients with central adrenal insufficiency manifest features of glucocorticoid and sex hormone deficiency. However, because the renin-angiotensin-aldosterone axis remains intact, these patients do not exhibit mineralocorticoid deficiency and, thus, tend not to present with acute life-threatening adrenal crises or electrolyte abnormalities. Additionally, hyperpigmentation is not a feature, as ACTH production is not increased. Symptoms of central adrenal insufficiency are otherwise similar to those seen in primary adrenal insufficiency.

**GENERAL APPROACH TO DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY**

**DIAGNOSIS**

**Cortisol Deficiency**

Cortisol levels are normally higher in the morning than in the afternoon and evening. For this reason, if adrenal hormone deficiency is suspected, a morning cortisol measurement is sometimes helpful. Any cortisol value (random or stimulated) greater than 18 µg/dL indicates adrenal sufficiency. Afternoon and evening cortisol levels are normally less than 9 µg/dL. Because cortisol is secreted in both a diurnal and pulsatile fashion, random cortisol levels are often less than 18 µg/dL, even during stress.

When adrenal insufficiency is suspected and if the clinical situation allows, a low-dose ACTH-stimulation test should be performed. The low-dose ACTH-stimulation test is reported to be 95% sensitive and 85% to 90% specific for adrenal insufficiency. The test can be performed at any time of day. Because the test bypasses the need for endogenous CRH and ACTH production because of the administration of exogenous ACTH, central CRH/ACTH insufficiency theoretically could yield a falsely normal result. However, in practice this is not the case, unless the hypothalamic and/or pituitary insult is very recent. A normal adrenal response to ACTH implies that the integrated hypothalamic-pituitary axis has been intact. To perform the low-dose ACTH-stimulation test, a baseline cortisol level is obtained, followed by intravenous (IV) administration of 1 µg of ACTH and remeasurement of cortisol levels every 10 minutes for 30 minutes. The biggest limitation with the test is its low specificity. Patients with borderline results may need subsequent testing using the high-dose ACTH-stimulation test.

**Mineralocorticoid Deficiency**

Electrolyte disturbances (hyponatremia, hyperkalemia) and elevated renin levels can indicate mineralocorticoid deficiency. Elevated renin levels occur early in response to hypovolemia and ongoing sodium loss/potassium retention; electrolyte changes reflected in laboratory measurements are a later-stage manifestation of mineralocorticoid deficiency.

**TREATMENT**

Treatment involves replacement of the hormones that are deficient. In primary adrenal insufficiency, both mineralocorticoid and glucocorticoids must be replaced. In central adrenal insufficiency, there is no need for mineralocorticoid replacement. The normal daily production of glucocorticoids may be lower than previously thought. In fact, stable isotope dilution studies have demonstrated that the daily production of cortisol is slightly less than 6 mg/m². Replacement doses are traditionally calculated using an estimate that approximately 50% of oral hydrocortisone is absorbed. However, recent studies suggest that absorption is in the 90% to 99% range.

**APPROACH TO SPECIFIC CAUSES OF ADRENAL INSUFFICIENCY: BRIEF CASES WITH DISCUSSION**

**CASE 1: NEONATAL FEMALE WITH AMBIGUOUS GENITALIA**

**Case 1 Presentation**

A 2-day-old female born with ambiguous genitalia is transferred to a neonatal intensive care unit for evaluation. The child was born at term without complications to nonconsanguineous parents. Birth weight was 3.56 kg (7.85 lb). The child has been tolerating feeds without difficulty. There are 2 older siblings who are healthy and growing well and who had no trouble regaining their birth weights. Extended family history is negative for neonatal deaths.

Physical examination reveals a weight of 3.45 kg (7.61 lb) and length at the 20th percentile. Vital signs are normal. General appearance is of an infant in no acute
distress. Genital examination reveals ambiguous genitalia, with clitoromegaly (chitoral index is 81 mm²) and pigmented, fused labia majora with a small vaginal sinus. External gonads are not palpable. Anogenital ratio is 0.73.

Initial laboratory evaluation reveals the following: serum sodium, 133 mEq/L; serum potassium, 5 mEq/L; serum bicarbonate, 24 mEq/L; plasma renin activity, 6585 ng/mL/hr (normal, full-term, day 1–7, 2–35 ng/mL/hr); and 17-hydroxyprogesterone, 1308.8 ng/dL (normal, 13–173 ng/dL). Karyotype analysis reveals a normal female karyotype (46,XX). Pelvic ultrasonography shows the presence of a uterus. Ovaries are not easily visualized ultrasonographically.

- **What is the presumptive diagnosis?**

The clinical finding of ambiguous genitalia in a newborn without palpable gonads should immediately raise suspicion for CAH and prompt an evaluation for adrenal insufficiency. Diagnosis of CAH is made on the basis of the clinical presentation and laboratory studies confirming elevated levels of hormones proximal to the enzymatic defect involved. The most common defect is 21-hydroxylase deficiency, in which case 17-hydroxyprogesterone levels will be elevated. A diagnostic ACTH-stimulation test (250 µg of cosyntropin) will reveal the pattern of adrenal hormone precursor elevation. Cortisol deficiency may also be seen. Electrolyte disturbances (hyponatremia, hyperkalemia) and elevated renin levels are consistent with salt-wasting and hypovolemia and indicate mineralocorticoid deficiency.

In the case patient, the combined findings of ambiguous genitalia, elevated 17-hydroxyprogesterone level, normal female karyotype, and the presence of a uterus on pelvic ultrasonography point strongly to classic CAH resulting from 21-hydroxylase deficiency. Although the patient does not yet exhibit the typical electrolyte disturbances seen in salt-wasting, the markedly elevated renin level is an early sign of aldosterone deficiency. About 75% of patients with classic 21-hydroxylase deficiency are also aldosterone-deficient and are at risk for salt-wasting crises associated with hyponatremia and dehydration. Adrenal crisis can present at several days to several weeks of life. In female infants, virilization or genital ambiguity may be the first indication of CAH, allowing for detection prior to adrenal crisis. Male infants, who have normal external genitalia at birth, are at higher risk for presentation with adrenal crisis.

**Case 1 Continued**

Confirmatory testing for 21-hydroxylase deficiency is obtained at 4 days of age. Results of high-dose (250 µg cosyntropin) ACTH-stimulation testing are shown in Table 4. Plasma renin activity remains elevated at 72.47 ng/mL/hr. Genetic studies confirm that the patient is a compound heterozygote for 2 common mutations in CAH; she carries one G allele and one null allele.

- **How should this patient be managed?**

Treatment for suspected CAH should be started as soon as blood samples have been obtained. Glucocorticoid replacement is important not only for regulation of carbohydrate metabolism and vascular tone but also to provide feedback to suppress the pituitary ACTH stimulation that is driving excessive adrenal androgen production. Critically ill patients require IV stress doses of hydrocortisone in association with IV fluids. Euvolemic patients can be treated with oral medications and fluids.

Replacement doses of hydrocortisone are generally 15 to 20 mg/m²/day in neonates; doses are 10 to 15 mg/m²/day later in life. During times of stress, including fever and surgery, stress doses of double to triple the daily dose are administered. Hydrocortisone is the preferred glucocorticoid preparation in young children. Its low potency allows for easier dose titration. Glucocorticoid overdosage leads to slow growth and excessive weight gain. Glucocorticoid undertreatment leads to excess androgen production that can result in advanced skeletal maturation, premature adrenarche, acne, and adult short stature in both males and females and hirsutism and infertility in females. Steroids with long durations of action, such as dexamethasone and prednisone, are typically avoided in growing children because of concerns for decreased growth velocity with overtreatment. However, in older adolescents or young adults, longer-acting glucocorticoids (eg, prednisone) can permit less frequent dosing.

Mineralocorticoid and salt supplementation are indicated for salt-wasting CAH. Fludrocortisone is usually administered at a dose of 0.1 to 0.3 mg daily. Neonates

<table>
<thead>
<tr>
<th>Hormone (units)</th>
<th>Baseline Value</th>
<th>Stimulated Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-OH-pregnenolone (ng/dL)</td>
<td>6215</td>
<td>52–828</td>
</tr>
<tr>
<td>17-OH-progesterone (ng/dL)</td>
<td>8644</td>
<td>13–173</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>&lt; 1</td>
<td>3–22</td>
</tr>
<tr>
<td>DHEA (ng/dL)</td>
<td>3681</td>
<td>26–505</td>
</tr>
<tr>
<td>DOC (ng/dL)</td>
<td>22</td>
<td>7–48</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone; DOC = 11-deoxycorticosterone; 17-OH-pregnenolone = 17-hydroxyprogrenolone; 17-OH-progesterone = 17-hydroxyprogesterone.
may require higher doses of mineralocorticoid because they tend to be mineralocorticoid-resistant and because markedly elevated levels of 17-hydroxyprogesterone act as competitive antagonists of the mineralocorticoid receptor. Salt supplementation (1–2 g/day) is usually recommended for infants and young children. Salt-wasting (hypovolemia) is a stress that contributes to ACTH release, subsequently leading to increased synthesis of adrenal androgens and other cortisol precursors. Thus, it is important to screen for mild subclinical mineralocorticoid deficiency, as mineralocorticoid treatment may allow for minimization of the glucocorticoid dose.

Therapy is guided by monitoring growth, pubertal onset and progression, and levels of precursor hormones (eg, 17-hydroxyprogesterone in 21-hydroxylase deficiency) in addition to adrenal androgens in virilizing CAH and plasma renin levels in salt-wasting CAH. The goal of therapy is to achieve normal puberty and growth; complete normalization of 17-hydroxyprogesterone is not the goal. Given that the gland is intrinsically abnormal, normal levels of 17-hydroxyprogesterone may not be achievable without glucocorticoid over-treatment. Finally, it is important to perform genetic testing in order to test family members who may be at risk.

Case 1 Conclusion

A urologic consult was obtained during the initial hospitalization to discuss the need for and timing of surgical procedures for feminizing genitoplasty, potentially including vaginoplasty and clitoral recession. Treatment for presumed CAH was initiated immediately after diagnostic testing was performed and consisted of mineralocorticoid replacement with fludrocortisone (0.1 mg) and glucocorticoid replacement with hydrocortisone. One month after glucocorticoid replacement was begun, repeat 17-hydroxyprogesterone levels had decreased to 402 ng/dL.

CASE 2: TEENAGE GIRL WITH PROGRESSIVE FATIGUE

Case 2 Presentation

A 14-year-old girl is brought by her mother to the emergency department with complaints of fatigue and decreased energy over the past several months in addition to numbness and tingling of her fingers.

The mother reports that her daughter had been growing well until recently, when she noted the girl’s growth began to slow. The patient experienced menarche at age 13, and her periods have been regular until the past few months. Past medical history reveals that the patient was healthy until the onset of her current complaints. There is no history of candidal infections and no history of polyuria or polydipsia. Review of systems is remarkable for increased tanning over the preceding summer months. Family history is positive for a 15-year-old brother with adrenal insufficiency, pernicious anemia, and keratoconjunctivitis.

Physical examination reveals a height of 150 cm, which is just below the 5th percentile, and a weight of 42 kg (92.6 lb), which is at the 10th percentile. General appearance is of a tanned, well-developed Hispanic female. Oral examination reveals no candidal lesions; gums are hyperpigmented. Neck examination shows no thyromegaly. The patient is Tanner stage IV for breasts and pubic hair. Skin examination reveals no pallor but rather hyperpigmentation, especially of the knees and knuckles. There are no skin lesions. Neurologic examination reveals positive Chvostek’s and Trousseau’s signs.

Laboratory evaluation reveals all electrolytes generally within normal limits: serum sodium is 134 mEq/L, serum potassium is 5.8 mEq/L, serum calcium is low at 6 mg/dL, and serum phosphorus is high at 8.4 mg/dL. The simultaneous intact parathyroid hormone is low at 1 pg/mL (normal, 7–53 pg/mL). Liver function tests are normal. Total thyroxine ($T_4$) is 7.8 µg/dL (normal, 5–12 µg/dL) and thyroid-stimulating hormone (TSH) is 2.28 µU/mL (normal, 0.3–5 µU/mL). The complete blood count is remarkable for eosinophilia and mild anemia, with a hematocrit of 31.9%. No Howell-Jolly bodies are seen on the smear.

Estrodiol is 20 pg/mL (normal, pubertal female, 30–100 pg/mL), luteinizing hormone (LH) is 10.6 mIU/mL (normal, 1–12 mIU/mL), and follicle-stimulating hormone (FSH) is 8 mIU/mL (normal, 1–12 mIU/mL). Low-dose ACTH-stimulation testing reveals a peak cortisol of 4.6 µg/dL. Plasma renin activity is 27.6 ng/mL/hr (normal, age 11–15 yr, normal sodium diet, supine, 0.5–3.3 ng/mL/hr). Antibody testing is positive for ovarian and thyroid antibodies but negative for antibodies directed against adrenal glands, pancreas, liver, intestines, and parathyroid glands.

The patient is diagnosed with hypoparathyroidism and adrenal insufficiency, with a presumed diagnosis of APS type 1. She is started on calcium and vitamin D along with hydrocortisone. Because her renin level is elevated, she is also started on fludrocortisone 100 µg/day. Two months after starting vitamin D therapy, the patient’s calcium and vitamin D levels remain low, and she is screened for deficiencies in other fat-soluble vitamins. She is found to be deficient in vitamins A and K and is begun on the combination of vitamins A, D, E, and K.

- How is the diagnosis of APS type 1 confirmed?
The diagnosis of APS type 1 should be suspected based on the presence of 2 or more of the following: candidiasis, hypoparathyroidism, adrenal insufficiency, pernicious anemia, or autoimmune thyroid disease. APS type 1 is now known to be caused by a mutation in the AIRE gene that codes for an autoimmune regulatory protein involved in peripheral immune tolerance. Associated autoimmune conditions seen in APS type 1 are shown in Table 3. Patients should be screened for antibodies against various intracellular enzymes present in multiple target organs: 21α-hydroxylase antibodies (adrenals); 17α-hydroxylase and side-chain cleavage enzyme antibodies (adrenals, gonads); GAD65 and tyrosine phosphatase-like protein IA-2 antibodies (pancreatic islets); tissue transglutaminase, tryptophane hydroxylase, hydrogen potassium ATPase, and intrinsic factor antibodies (stomach, intestines); thyroid peroxidase and thyroglobulin antibodies (thyroid); CYP1A2, CYP2A6, and aromatic L-amino acid decarboxylase antibodies (liver); and tyrosine hydroxylase antibodies (hair follicles). Parathyroid antibodies directed against the calcium-sensing receptor (CaSR) are often negative in APS type 1, even in parathyroid disease, as they were in this patient. Complete blood counts should include smears looking for Howell-Jolly bodies (indicative of asplenism).

Management of APS type 1 includes vigilant observation for oral candidiasis, which can predispose to oral cancer over time. Intense control of oral Candida (eg, amphotericin lozenge, fluconazole or ketoconazole if needed) and prompt biopsy of suspicious lesions are indicated. Careful mouth hygiene, smoothing of sharp points of teeth, and elimination of plastic materials from the mouth also are important. If the patient is hypoparathyroid, calcium should be checked every 6 to 8 weeks. Patients should not receive live virus immunizations.

Case 2 Conclusion

AIRE gene testing in the patient and her brother reveals a homozygous mutation termed c. 967del13 in exon 8 of the AIRE gene, which is one of the known mutations commonly seen in APS type 1. The patient is monitored for the development of additional autoimmune problems. She is also monitored closely for the development of keratoconjunctivitis, gallstones, asplenia, diabetes.

CASE 3: NEAR Born MALE WITH PERSISTENT HYPOGLYCEMIA

Case 3 Presentation

A male infant born at term without complications to a 16-year-old mother experiences a seizure at 2 days of age associated with a serum glucose level of 6 mg/dL. An endocrinology consult is obtained at day 7 of life for persistent hypoglycemia. There is no history of maternal diabetes.

Physical examination reveals an infant in no distress. Weight, length, and head circumference are each at the 50th percentile. Direct and consensual responses to light are present but sluggish. There is no nystagmus. There are no midline facial defects. Palate is intact. There is no hepatomegaly. Stretched penile length is 2.1 cm, with bilaterally descended testes. The patient is generally noted to be jaundiced, with scleral icterus.

Laboratory studies obtained on day 6 of life reveal normal levels of electrolytes, urine organic acids, and plasma amino acids as well as the following: serum glucose, 21 mg/dL (normal, neonate, 40–110 mg/dL); indirect bilirubin, 7.7 mg/dL (normal, 0–10.5 mg/dL); direct bilirubin, 2.7 mg/dL (normal, 0–0.6 mg/dL); alkaline phosphatase, 452 U/L (normal, 110–320 U/L); TSH, 8.97 µIU/mL; free T4, 0.7 ng/dL (normal, 0.8–1.9 ng/dL); total T4, 4.4 µg/dL; LH, 0.2 mIU/mL; FSH, 0.7 mIU/mL; and testosterone, < 4 ng/dL (normal 75–400 ng/dL). A blood sample drawn when the patient’s serum glucose is 21 mg/dL reveals the following: cortisol, < 1 µg/dL; insulin, < 2 µU/mL; and GH, 2 ng/mL.

The patient is initially treated with frequent feedings (every 3 hours) in addition to a continuous IV infusion of dextrose, which was started after the seizure. Weaning of dextrose is not possible, as his serum glucose levels remain in the 50 to 60 mg/dL range.

- What is the differential diagnosis in this case?

This male infant presents with persistent severe hypoglycemia, jaundice, and microenopis (defined as a stretched penile length < 2.5 cm at term). These findings suggest the presence of multiple pituitary hormone deficiencies: cortisol and GH deficiencies leading to hypoglycemia, GH and thyroid hormone deficiencies contributing to jaundice, and gonadotropin (LH, FSH) deficiency associated with microenopis. The critical blood sample drawn during hypoglycemia reveals an appropriately suppressed insulin level less than 2 µU/mL but inappropriately low levels of cortisol and GH. A GH level greater than 10 ng/mL and a cortisol level greater than 18 µg/dL during hypoglycemia would confirm GH sufficiency and adrenal sufficiency. The low levels of free and total T4 with only a mildly elevated TSH are consistent with central hypothyroidism. Gonadotropin deficiency is suspected based on the undetectable testosterone level in the absence of a marked elevation in LH and FSH. The infant does not exhibit hepatomegaly, making the common forms of glycogen storage disease
and defects in gluconeogenesis unlikely. There is no acidosis, and the evaluation for metabolic disorders (including urine organic acids and plasma amino acids) is negative.

**Case 3 Conclusion**

Glucagon/arginine GH-stimulation testing elicits a low peak GH level of 5.5 ng/mL, and low-dose (1 µg) ACTH-stimulation testing elicits a low peak cortisol level of less than 1 µg/dL. These results confirm the diagnosis of hypopituitarism. Magnetic resonance imaging of the head reveals a small adenohypophysis with thin pituitary infundibulum, hypoplastic optic nerves, and cavum septum pellucidum, findings consistent with septo-optic dysplasia.

Hormone replacement therapy with GH, thyroid hormone, and maintenance glucocorticoids is initiated. The jaundice gradually improves and the patient is able to be weaned off the IV glucose infusion. A series of 3 low-dose testosterone injections is begun for phallic enlargement.

- **How should this patient be treated and monitored?**

  This patient will require continued hormone replacement (thyroid hormone, GH, glucocorticoids) throughout life, with stress dosing of glucocorticoids in times of illness, fever, or surgery. Additionally, the patient will require testosterone replacement in increasing doses to mimic normal pubertal physical changes. As with any child with hypothalamic-pituitary defects, this patient is at risk for development of diabetes insipidus, and the family should be instructed to monitor his urine output.

  The prognosis for patients with hypopituitarism associated with septo-optic dysplasia can be excellent if hormone deficiencies are detected early and are normalized. The degree of visual impairment varies widely; close follow-up by an ophthalmologist is indicated.

**REFERENCES**


