

# Pediatrics<sup>in</sup>Review<sup>®</sup>

## **Congenital Adrenal Hyperplasia : Diagnosis, Evaluation, and Management**

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# Congenital Adrenal Hyperplasia: Diagnosis, Evaluation, and Management

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Author Disclosure  
Drs Antal and Zhou have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Describe the pathophysiology of congenital adrenal hyperplasia (CAH).
2. Characterize the signs and symptoms of CAH.
3. Describe the appropriate laboratory evaluation of CAH.
4. Know that CAH can be diagnosed prenatally.
5. Recognize adrenal insufficiency by laboratory and clinical evaluation.
6. Anticipate and plan treatment for both acute adrenal crisis and long-term therapy for a patient who has CAH.
7. Discuss the value of newborn screening for salt-losing CAH in male infants.

## Introduction

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders of adrenal steroidogenesis. The common functional defect in each disorder is impaired cortisol secretion, resulting in hypersecretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) and consequent hyperplasia of the adrenal glands. More than 90% of cases of CAH are caused by a defect in the enzyme 21-hydroxylase (21-hydroxylase deficiency [21OHD]). Four other enzyme deficiencies in the steroid biosynthesis pathway, along with one cholesterol transport protein defect, account for the remaining cases. Depending on the severity of the enzyme deficiency, 21OHD is defined as classic (severe form) or nonclassic (mild form). Approximately 75% of patients who have the classic form also have salt wasting due to inadequate aldosterone production, further subdividing the classification into classic simple virilizing and classic salt-wasting forms. This review highlights the diagnosis and treatment of 21OHD, with a brief discussion of the other forms of CAH.

## Case Presentation

*A Hispanic baby girl is born at term, has a birthweight of 3.1 kg, and has ambiguous genitalia (Fig. 1). During the first week after birth, the baby is clinically stable but demands frequent feeding. On the sixth postnatal day, serum electrolyte measurements are normal. Additional evaluation reveals female internal organs on pelvic ultrasonography and female karyotype. Newborn screening results show 17-hydroxyprogesterone (17-OHP) values of 180 and 679 ng/mL 2 and 5 days after birth, respectively. Serum hormones measured on postnatal day 6 show marked elevations of 17-OHP at 34,700 ng/mL and androstenedione at 2,445 ng/mL, with a low cortisol value of 1.1 mcg/dL (30.3 nmol/L). On postnatal day 8 (the same day the newborn screening results first became available), the baby experiences a salt-wasting crisis, presenting with one episode of vomiting, dry mucous membranes, and decreased blood pressure. Her biochemical profile is shown in Table 1. She is treated successfully with aggressive hydration via normal saline, along with stress doses of hydrocortisone and glucose supplementation.*

## Abbreviations

<b>ACTH:</b>	adrenocorticotrophic hormone
<b>AMH:</b>	anti-Müllerian hormone
<b>CAH:</b>	congenital adrenal hyperplasia
<b>CRH:</b>	corticotropin-releasing hormone
<b>DHEA:</b>	dehydroepiandrosterone
<b>DHT:</b>	dihydrotestosterone
<b>IV:</b>	intravenous
<b>PRA:</b>	plasma renin activity
<b>17-OHP:</b>	17-hydroxyprogesterone
<b>21OHD:</b>	21-hydroxylase deficiency

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**Figure 1.** External genitalia of female infant affected with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Note complete fusion of the labioscrotal folds and a male penile appearance without testes.

*Genetic testing confirms the diagnosis of the salt-wasting form of 21OHD.*

### Adrenal Steroidogenesis

The adrenal gland is composed of the cortex and medulla. The inner medulla, composed of neuronal tissue, is the site of catecholamine production; the outer adrenal cortical glandular tissue is the production site for three classes of steroid hormones: mineralocorticoids, glucocorticoids, and sex hormones. The cortex is divided into three zones by different cellular arrangements, each one functionally distinct due to the enzymes required for different hormone production. The outer zona glomerulosa synthesizes mineralocorticoids. This zone is regulated primarily by angiotensin II, which stimulates

growth of the zone as well as synthesis of aldosterone, the most potent mineralocorticoid. The middle zona fasciculata produces glucocorticoids, and the inner zona reticularis synthesizes androgens, along with a small amount of glucocorticoids. The two inner zones are regulated primarily by ACTH, which stimulates the growth of both zones along with synthesis of cortisol (the most potent glucocorticoid) and androgens.

The biochemical pathways of adrenal steroidogenesis are shown in Fig. 2. The steroidogenic acute regulatory protein (StAR) carries cholesterol to the inner mitochondrial membrane. Cortisol subsequently is produced in the zona fasciculata in five steps. The first step is cleavage of the cholesterol side chain by the cholesterol desmolase enzyme to yield pregnenolone. Pregnenolone is the common precursor for all other steroids. The next step is conversion of pregnenolone to progesterone by 3-beta-hydroxysteroid dehydrogenase. The successive three steps are sequential hydroxylations at the 17-alpha, 21, and 11-beta positions, resulting in cortisol synthesis.

Although the adrenal medulla and cortex are derived from completely different tissues and secrete different hormones, evidence suggests an interrelationship between the two. The enzyme phenylethanolamine N-methyltransferase, which mediates the final step of epinephrine synthesis (converting norepinephrine to epinephrine), is induced by high local concentrations of cortisol. In the absence of adrenal cortisol production, epinephrine synthesis is decreased, and patients may present with catecholamine-resistant hypotension.

For patients afflicted with 21OHD, impaired conversion of progesterone to deoxycorticosterone results in aldosterone (mineralocorticoid) deficiency, and impaired conversion of 17-OH progesterone to 11-deoxycortisol results in cortisol (glucocorticoid) deficiency. The reduced cortisol production causes hypersecretion of CRH and ACTH through the negative feedback mechanisms of the hypothalamic-pituitary-adrenal axis. The excess accumulated precursors proximal to the 21-hydroxylation step shunt into the sex steroid pathway, resulting in increased androgen production.

### Sex Differentiation

A sex-determining region on the Y chromosome is required for differentiation of testes from the early bipotential gonads between 6 and 8 weeks of gestation. Fetal internal and external genitalia initially are bipotential, with the presence of both Wolffian and Müllerian ducts presenting the potential for developing male or female internal genitalia, respectively. Whether male or female internal genitalia develop depends on the presence of two

#### Table 1. The Biochemical Profile

- Sodium: 128 mEq/L (128 mmol/L)
- Potassium: 7.1 mEq/L (7.1 mmol/L)
- Chloride: 88 mEq/L (88 mmol/L)
- Bicarbonate: 13 mEq/L (13 mmol/L)
- Blood urea nitrogen: 33 mg/dL (11.8 mmol/L)
- Creatinine: 0.9 mg/dL (79.6 mcmol/L)
- Glucose: 40 mg/dL (2.2 mmol/L)

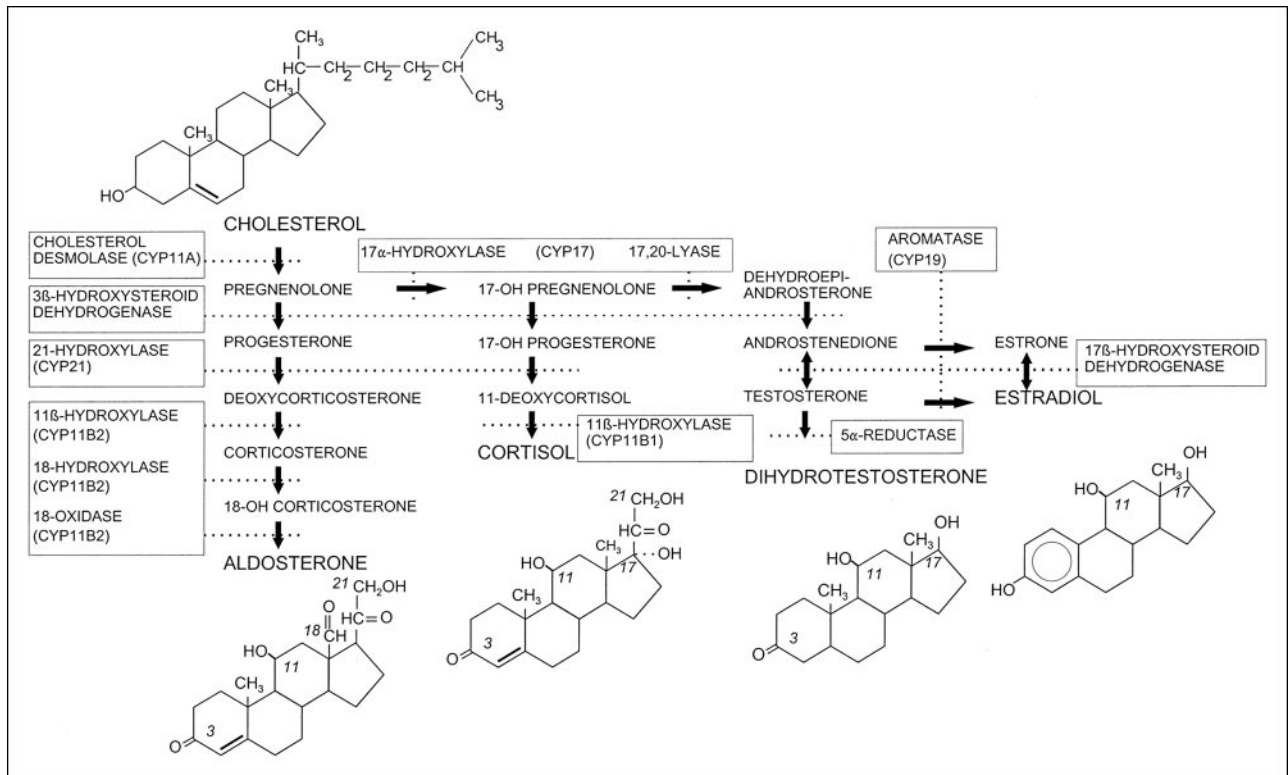


Figure 2. Pathways of steroid biosynthesis. The pathways for synthesis of progesterone and mineralocorticoids (aldosterone), glucocorticoids (cortisol), androgens (testosterone and dihydrotestosterone), and estrogens (estradiol) are arranged from left to right. The enzymatic activities catalyzing each bioconversion are written in boxes. For those activities mediated by specific cytochromes P450, the systematic name of the enzyme ("CYP" followed by a number) is listed in parentheses. CYP11B2 and CYP17 have multiple activities. The planar structures of cholesterol, aldosterone, cortisol, dihydrotestosterone, and estradiol are placed near the corresponding labels. Adapted from White et al, 2000.

hormones produced by the fetal testis: testosterone, secreted by the Leydig cells, and anti-Müllerian hormone (AMH), secreted by the Sertoli cells. By 8 weeks of gestation, a normal male fetus is able to secrete these two hormones.

High amounts of local testosterone secreted by the testes direct the formation of the internal male urogenital tract from the Wolffian ducts. AMH suppresses development of the Müllerian ducts, thus preventing formation of the female internal structures, including the fallopian tubes, uterus, cervix, and upper vagina. In a female fetus, the absence of high local testosterone concentrations and AMH causes the Wolffian ducts to regress and Müllerian ducts to develop, respectively. The differentiation of male external genitalia and the urogenital sinus is affected by dihydrotestosterone (DHT), a more potent male hormone derived from testosterone by 5- $\alpha$ -reductase conversion during the critical period of 8 to 12 weeks of gestation. In the presence of DHT, the genital tubercle, genital fold, genital swelling, and urogenital sinus be-

come the penis, scrotum, and prostate, respectively. In the absence of DHT, the genital tubercle, genital fold, genital swelling, and urogenital sinus develop into the clitoris, labia minora, labia majora, and lower third of the vagina.

In male patients born with CAH, genitalia usually are unaffected by the excess adrenal androgens because they normally have a higher level of testosterone production from the testes. In female fetuses, however, external genitalia can be virilized to varying degrees. However, even in severely virilized females, the internal genitalia still are normal.

## Genetics

The overall incidence of CAH due to 21OHD is approximately 1 in 16,000, with variations seen in different ethnic and racial groups. The inheritance is autosomal recessive. The activity of 21-hydroxylase is mediated by cytochrome p450c21, found in the endoplasmic reticulum. The 21-hydroxylase genes (*CYP21*) lie within the

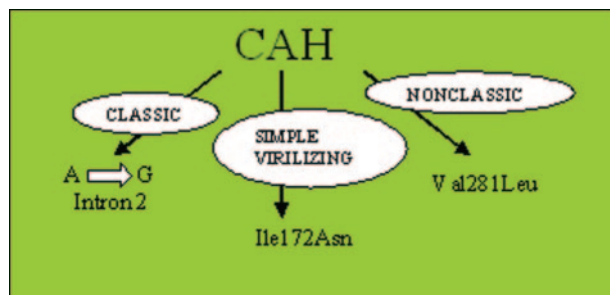


Figure 3. Microconversions from alanine (A) to glycine (G) in intron 2, from isoleucine (Ile) to asparagine (Asn) in exon 4, and from valine (Val) to leucine (Leu) in exon 7 are the most common mutations in the classic salt-wasting, simple virilizing, and nonclassic forms of CAH, respectively.

class III region of the human major histocompatibility complex on chromosome 6. The *CYP21* gene structure contains both *CYP21* and a pseudogene (*CYP21P*). The two genes are highly homologous, but only the *CYP21* gene is active. The *CYP21P* gene has numerous deleterious mutations that are inconsistent with normal gene expression. Most mutations causing 21OHD result from recombinations between *CYP21* and the pseudogene. In general, the correlation between genotype and phenotype is high. Multiple gene defects have been found; the most common mutations in the respective clinical forms are shown in Fig. 3. Most individuals born with 21OHD are compound heterozygotes, that is, each copy of their *CYP21* genes has a different mutation or deletion. Typically, both abnormal genes are inherited from the parents (one from each), although 1% of affected individuals have only one parent who is a carrier. In these cases, the second mutation is spontaneous.

Molecular genetic testing of the *CYP21* gene is available commercially and has the ability to detect common mutations and deletions in the different forms in up to 95% of affected individuals.

### Clinical Features

Excessive androgen production is the hallmark of this disorder. In the severe classic form, genital ambiguity is present in affected female infants. In fact, 21OHD has been recognized as the most common cause of ambiguous genitalia in a genetically female fetus. The phenotypic virilization varies from simple clitoromegaly, with or without partial fusion of the labioscrotal folds, to the appearance of a penile urethra. Although the genitalia of a female born with the severe form of the disease may be indistinguishable from that of a male, the important differentiating points are the absence of testes and presence of normal uterus and ovaries.

In newborn males, the external genitalia usually are unaffected, except for subtle penile enlargement. Genitalia may continue to virilize postnatally. Other common signs of hyperandrogenism in childhood include early appearance of axillary and pubic hair, acne, and adult body odor. The high concentrations of androgens accelerate growth, resulting in tall and muscular features in early childhood. However, affected children's final adult heights are compromised due to advanced bone age associated with premature epiphyseal closure.

Approximately 75% of patients who have classic CAH due to 21OHD have a deficiency of aldosterone (classic salt-wasting form). Unlike those who have the simple virilizing form, who present with only virilization, these patients present with salt-wasting and acute adrenal crisis, often within the first few weeks after birth. Table 2 lists the typical signs and symptoms of acute adrenal crisis in CAH. Hyperpigmentation of skin creases and genitalia may be early signs of adrenal insufficiency. Of note, affected infants initially demand frequent feedings, possibly due to dehydration or salt craving. Poor feeding is a late sign of CAH and severe adrenal crisis.

Nonclassic 21OHD may be the most common autosomal recessive disorder in humans. Its prevalence rate is approximately 3.7% (1 in 27) in Ashkenazi Jews and 0.1% (1 in 1,000) in white populations. In this disorder, partial deficiency of 21-hydroxylation results in milder symptoms of the disease. Genital ambiguity is not present at birth, and androgen excess manifests later in life for both males and females. In the early ages, presentations include premature adrenarche and an advanced bone age.

### Table 2. Typical Signs and Symptoms of Acute Adrenal Crisis

- Decreased activity/fatigue
- Altered sensorium/unresponsiveness
- Poor feeding/weak suck
- Dry mucous membranes
- Hyperpigmentation
- Abdominal pain
- Vomiting
- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Metabolic acidosis
- Hypothermia
- Hypotension
- Dehydration
- Lack of weight gain

### Table 3. Initial Important Laboratory Evaluation

- Glucose/dextrose stick at bedside
- Chem-20 (including electrolytes and liver function panel)
- Arterial blood gas/serum pH
- Cortisol
- ACTH
- 17-OHP
- Pelvic ultrasonography
- Karyotype

In adolescent females, hirsutism, male-pattern baldness, oligomenorrhea or amenorrhea, and polycystic ovary disease may occur. In both males and females, short adult stature, insulin resistance, and severe cystic acne are common.

### Biochemical and Hormonal Studies

Table 3 lists the most important initial laboratory evaluation for patients suspected of experiencing adrenal crisis due to 21OHD. It is critical to assure that the potassium concentration is obtained from a nonhemolyzed sample to minimize the likelihood of a falsely elevated potassium value.

To evaluate adrenal function and differentiate among the various potential enzymatic defects, an ACTH stimulation test should be performed. Administration of 0.25 mg of cosyntropin (a synthetic ACTH) provides a pharmacologic stimulus to the adrenal glands, maximizing hormone secretion. A full adrenal profile, including measurement of 17-OHP, cortisol, deoxycorticosterone, 11-deoxycortisol, 17-hydroxypregnenolone, dehydroepiandrosterone (DHEA), and androstenedione, should be obtained immediately prior to and 60 minutes after cosyntropin administration. Measurements of enzyme products, precursors, and ratios of precursors to products are critical in distinguishing among the different enzymatic defects. If blood volume is of concern in small infants, a single sample collected at the 60-minute time point is most valuable. For evaluation of possible 21OHD, this sample should include 17-OHP, cortisol, and androstenedione. If the diagnosis remains unclear, it may be desirable to treat the child and retest after partially or completely tapering glucocorticoids.

The different forms of CAH due to 21OHD may be determined based on baseline and stimulated values of 17-OHP, the immediate precursor to the 21-hydroxylase enzyme, although overlaps may exist (Fig. 4).

Elevated plasma renin activity (PRA) values, particularly the ratio of PRA to aldosterone, are markers of impaired mineralocorticoid synthesis. Additional tests for evaluation of ambiguous genitalia include a rapid karyotype and pelvic and abdominal ultrasonography. Rapid identification of internal structures such as a uterus or ovaries via ultrasonography may be particularly helpful in the often stressful initial period, when both parents and clinicians are seeking rapid answers. Additional testing may be required, depending on the outcome of initial tests. For example, a radiologic dye study to evaluate internal genitourinary anatomy may be performed for infants who have a 46XX karyotype.

### Treatment

#### Acute Adrenal Crisis

Acute adrenal insufficiency is a medical emergency. Patients experiencing an adrenal crisis virtually always have significant volume contraction, and initial management should consist of fluid resuscitation with a 20-mL/kg bolus of 0.9% normal saline. Repeated boluses may be needed. Replacement of fluid losses should be continued with isotonic crystalloid solutions containing dextrose (typically 5% dextrose with normal saline) at a rate of 1.5 to 2 times maintenance. Stress doses of hydrocortisone (100 mg/m<sup>2</sup> per day) are vital in the management and should be given as early as possible, concomitant with intravenous (IV) fluid treatment. Central venous

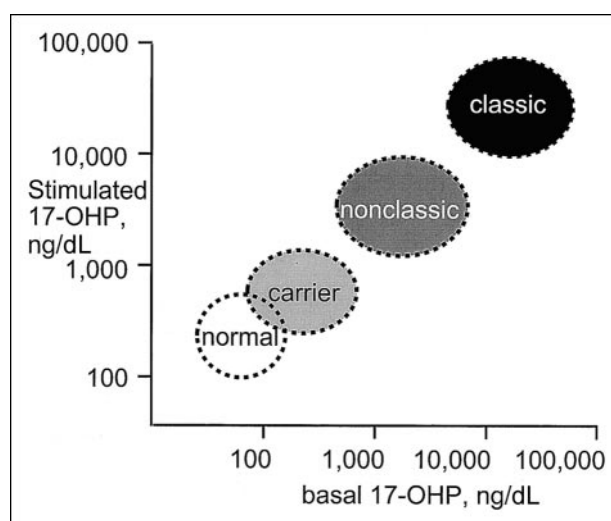


Figure 4. Nomogram for comparing 17-OHP values before and 60 minutes after administration of a 0.25-mg intravenous bolus of cosyntropin in patients with and without 21OHD. Note that values for normal and heterozygote (carrier) overlap. Reprinted with permission from White et al, 2000.

access and vasopressors, along with higher glucose concentrations, may be required in profoundly ill patients. Life-threatening hyperkalemia may require additional therapy with potassium-lowering resin, IV calcium, insulin, and bicarbonate.

### Long-term Management

All patients who have classic 21OHD and symptomatic patients who have nonclassic disease require glucocorticoids to suppress the excessive secretion of CRH and ACTH and reduce the abnormally high serum concentrations of adrenal androgens. In children, the preferred cortisol replacement is oral hydrocortisone, in three divided doses of 10 to 20 mg/m<sup>2</sup> per day. Hydrocortisone is the treatment of choice due to its short half-life and minimal growth suppressive effect. Treatment efficacy is assessed by monitoring ACTH, 17-OHP, DHEA, and androstenedione. A target 17-OHP range of 500 to 1,000 ng/dL, although still higher than normal, helps to avoid the adverse effects of overtreatment. Hormones should be measured, preferably at 8 AM, just before the next dose is due. Patients should be monitored carefully for signs of iatrogenic Cushing syndrome, including rapid weight gain, poor growth velocity, hypertension, pigmented striae, and osteopenia. Children also should have an annual bone age radiograph and careful monitoring of linear growth. Advanced bone age and increased growth velocity should alert pediatricians to undertreatment. In older children and adolescents, where growth is complete, once-daily dexamethasone offers a simpler dosing regimen and may be considered instead of hydrocortisone for improved compliance.

Patients who have classic CAH cannot mount a sufficient cortisol response to stress and require pharmacologic doses of hydrocortisone in situations such as febrile illness, trauma, and surgery under general anesthesia. During times of mild-to-moderate stress, such as fever, dosing guidelines suggest doubling or tripling the usual maintenance dose of oral hydrocortisone. Emergency injectable hydrocortisone must be available in case of vomiting. For severe stress and major surgery, administration of hydrocortisone (100 mg/m<sup>2</sup> per day), divided in three to four IV doses, is warranted for at least 24 hours peri- and postoperatively before tapering over several days to a maintenance dose. Patients and parents should receive instructions about stress dose coverage, and every patient should wear a medical alert bracelet or necklace and carry the emergency medical information card that is supplied with it.

Infants born with the salt-wasting form of 21OHD require replacement with fludrocortisone, the only com-

mercially available mineralocorticoid, along with sodium chloride supplements. The dose of fludrocortisone is usually 0.1 to 0.2 mg, but occasionally patients require up to 0.4 mg/day. Supplementation with 1 to 2 g of sodium chloride often is required (each gram of sodium chloride contains 17 mEq of sodium). The sodium content of human milk or most infant formulas is about 8 mEq/L. Considerably more sodium (8 mEq/kg per day) must be supplemented to keep up with ongoing losses. Often, older children acquire a taste for salty foods and no longer require daily supplements of sodium chloride tablets. Moreover, fludrocortisone doses often may be decreased after early infancy. PRA can be used to monitor the effectiveness of mineralocorticoid and sodium replacement. Hypertension, tachycardia, and suppressed PRA production are clinical signs of overtreatment. Excessive increases in fludrocortisone dosage also may retard growth.

### Genitalia Surgery

Affected female infants may require surgical reconstruction, with reduction clitoroplasty and construction of a vaginal opening. Later revision may be required. With appropriate management, a normal sex life and fertility may be expected.

### Prenatal Diagnosis and Treatment

Both molecular genetic testing of the fetus and prenatal treatment of mothers with dexamethasone are available. Dexamethasone must be given before the seventh to eighth week of gestation to suppress the fetal pituitary-adrenal axis before virilization occurs. Approximately 70% of prenatally treated females are born with normal or only slightly virilized genitalia. For couples known to be carriers or those who have had an affected child in the past, oral dexamethasone should be offered to the pregnant woman after conception and before 10 weeks' gestation. Fetal cells can be sampled either by chorionic villous sampling (at 10 to 12 weeks' gestation) or amniocentesis (at 14 to 18 weeks' gestation), and the specimen should be sent for chromosome analysis. If the fetus is male, dexamethasone therapy is discontinued. If the fetus is female, additional molecular genetic testing is performed on the sample to determine if she has 21OHD. If the fetus is affected, maternal dexamethasone administration is continued to term; if not, it can be discontinued. Due to the common adverse effects of dexamethasone on the mother and the potential for congenital malformations in the fetus, prenatal treatment remains experimental.

## Newborn Screening

Screening programs for CAH were developed primarily to identify cases in male infants of the salt-wasting type of classic 21OHD, where clinicians may not be alerted to the disorder given the lack of genital ambiguity. Newborn screening also helps avoid incorrect sex assignment in newborn females born with severe virilization. Most states in the United States include CAH in their newborn screening panels by measuring 17-OHP concentrations using filter paper blood collection cards, which also are used to screen for hypothyroidism, phenylketonuria, and other disorders.

To achieve higher sensitivity in detection, a low 17-OHP cut-off value typically is used. Preterm, sick, or stressed infants tend to have higher 17-OHP values, even when corrected for birthweight. The specificity of the test is only 2%, which translates to a very high false-positive rate of 98%. Pediatricians should be aware that despite the high sensitivity, false-negatives can occur. Protocols to follow up positive results vary from state to state. Usually, both the infant's primary physician and a pediatric endocrinologist are notified of the abnormal newborn screening results. Generally, cases manifesting with mildly elevated 17-OHP values (40 to 100 ng/mL for term infants) can be followed up with a repeat filter paper specimen. Infants having higher values are evaluated via determination of electrolytes and a serum 17-OHP concentration. If elevated potassium and decreased

sodium concentrations are found, the same treatment indicated for an acute adrenal crisis should be started immediately while waiting for confirmatory laboratory studies, and a pediatric endocrinologist should be consulted for additional management. If the initial electrolyte values are normal, patients still should be followed closely until results of studies of steroid precursors have returned because decompensation from salt loss sometimes occurs later in the first postnatal month. If 17-OHP and other steroid precursors are not unequivocally normal, the infant should be referred to a pediatric endocrinologist for additional testing via a cosyntropin-stimulated adrenal profile or genetic testing.

## Differential Diagnosis of Different Forms of CAH

Five genetic mutations in the cortisol biosynthesis pathway, four (*CYP21*, *CYP17*, *CYP11B1*, *HSD3B2*) that encode enzymes for steroid hormone synthesis, and one *StAR* that encodes the intracellular cholesterol transport protein, can cause CAH. Because a cytochrome P450scc (*CYP11A*) mutation is believed to be incompatible with life, and only one case of late-onset disease due to a heterozygous mutation has been reported, this disorder is not included in this section. Distinctive biochemical consequences and clinical features resulting from different mutations are listed in Table 4.

All disorders listed have autosomal recessive inheri-

Table 4. Characteristics of Different Forms of Congenital Adrenal Hyperplasia (CAH)

	21-Hydroxylase Deficiency	11-beta Hydroxylase Deficiency	17-alpha-Hydroxylase Deficiency	3-beta-Hydroxysteroid Dehydrogenase Deficiency	Lipoid CAH
Incidence	1:10 to 18,000	1:100,000	Rare	Rare	Rare
Gene involved	<i>CYP21</i>	<i>CYP11B1</i>	<i>CYP17</i>	<i>HSD3B2</i>	<i>StAR</i>
Chromosomal location	6p21.3	8q24.3	10q24.3	1p13.1	8p11.2
Ambiguous genitalia	Yes in females	Yes in females	Yes in males	Yes in males	Yes in males
Adrenal crisis	Yes	Rare	No	Yes	Yes (severe)
Glucocorticoid values	↓	↓	↓	↓	↓
Mineralocorticoid values	↓	↑	↑	↓	↓
Androgens	↑	↑	↓	↑ in females ↓ in males	↓
Sodium concentrations	↓	↑	↑	↓	↓
Potassium concentrations	↑	↓	↓	↑	↑
Metabolite elevated	17-OHP	DOC, 11-deoxycortisol	DOC, corticosterone	DHEA, 17-hydroxypregnenolone	None

DHEA=dehydroepiandrosterone, DOC=deoxycorticosterone, 17-OHP=17-hydroxyprogesterone, StAR=steroidogenic acute regulatory protein



tance. Only 21OHD and 11-beta hydroxylase deficiency are predominantly virilizing disorders. Patients who have the remaining disorders have impaired production of both cortisol by the adrenals and gonadal steroids. Male patients exhibit varying degrees of undervirilization caused by deficient testosterone production by the fetal Leydig cells; female patients may or may not exhibit virilization. If present in the female cases, virilization is much less severe than in 21OHD and 11-beta OHD. Because clinical features may appear similar in these cases, a comparison of precursor-to-product ratios by ACTH-stimulated adrenocortical profile and sometimes genetic tests are required for correct diagnosis of each distinct disorder.

### Long-term Outcome

Glucocorticoid treatment for CAH was introduced in 1950. Experience with its long-term outcomes is still accumulating. Children who have CAH often are tall in early childhood, but ultimately are short in adulthood. Recent data suggest that patients born with CAH are about 10 cm shorter than their parentally based targets. Advanced bone age and central precocious puberty due to androgen excess causing early epiphyseal fusion are the primary factors. In addition, treatment of CAH with glucocorticoids can suppress growth and diminish final height. Experimental treatment with growth hormone and luteinizing hormone-releasing hormone analog (to hold off puberty) are reported to lead to an average height gain of 7.3 cm.

Both male and female patients are fertile but have reduced fertility rates. This consequence is due to biologic, psychological, social, and sexual factors. The reported biologic causes for females include inadequate vaginal introitus, poor adrenal suppression, high prevalence of polycystic ovary syndrome, and elevated follicular phase progesterone concentrations causing failure of implantation. In males, biologic causes include the presence of adrenal rest tissue and luteinizing hormone suppression, leading to hypogonadotropic hypogonadism due to inadequate adrenal suppression. Leydig cell malignancy also has been reported in males who have CAH.

Cognitive functions are normal in those who have CAH. In virilized females, brains are “hardwired” by male hormones during the critical period. With respect to sex identity, women who have CAH tend to self-identify as female, with few exceptions. As for sexual orientation, reported rates of homosexuality and bisexuality are less consistent and vary as widely as 5% to 37%. More consistent evidence regarding the effects of andro-

gens comes from gendered play activities of young children. Girls exposed to high amounts of prenatal androgen are more likely to prefer “boy toys” such as cars and guns instead of “girl toys” such as dolls and kitchen equipment.

Bone density is reported to be normal in most patients. The prevalence of metabolic abnormalities such as obesity, insulin resistance, dyslipidemia, and polycystic ovarian syndrome has been reported to be high due to the diseases themselves or glucocorticoid treatment.

## Summary

- CAH represents a family of disorders of the cortisol synthesis pathway in which more than 90% of cases are caused by 21OHD. The hallmark of 21OHD is excessive androgen production that varies in degree among its different subtypes.
- The severe classic form of CAH is the most common cause of ambiguous genitalia in a genetically female fetus.
- Experimental treatment of mothers with dexamethasone in early gestation results in significantly less virilization in female fetuses affected with classic CAH.
- Newborn screening has had an important impact on identifying the salt-wasting subtype in male infants and preventing adrenal crisis.
- Lifelong treatment with steroids is required for most patients.
- The consequences of the disease and complications of the treatment remain a challenge and require the involvement of multiple subspecialties.
- As in many other diseases, gene therapy offers real hope for a cure for CAH.

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