REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

Deborah P. Merke, M.D., and Richard J. Auchus, M.D., Ph.D.

From the National Institutes of Health Clinical Center and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (D.P.M.); and the Division of Metabolism, Endocrinology, and Diabetes and the Departments of Internal Medicine and Pharmacology, University of Michigan, Ann Arbor (R.J.A.). Address reprint requests to Dr. Merke at the National Institutes of Health Clinical Center, Bldg. 10, Rm. 3-2740, 10 Center Dr., MSC 1932, Bethesda, MD 20892-1932, or at dmerke@nih.gov.

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CONGENITAL ADRENAL HYPERPLASIA (CAH) — ONE OF THE MOST COMMON autosomal recessive disorders — is potentially life-threatening in its classic (severe) form and may be asymptomatic or cause female infertility in its nonclassic (mild) form. The most common type of CAH is 21-hydroxylase deficiency[1]; for the remainder of this review, CAH indicates CAH due to 21-hydroxylase deficiency.

CAH is a disease of multiple hormonal imbalances. Mutations in *CYP21A2* (the gene encoding 21-hydroxylase, a cytochrome P-450 enzyme) result in lack of 21-hydroxylase, which is required for the production of cortisol and aldosterone in the adrenal cortex. A deficiency of this enzyme has cascading effects. Reduced cortisol leads to overproduction of pituitary corticotropin, which stimulates the accumulation of cortisol precursors and their subsequent diversion through the steroid pathways that produce adrenal androgens. Today, the classic form is the most common cause of atypical genitalia in 46,XX newborns and of primary adrenal insufficiency during childhood.[2,3]

A continuum of disease phenotypes generally correlates with *CYP21A2* genotypes and the expected residual 21-hydroxylase activity with each genotype.[1,4] Hormonally based, lifesaving neonatal screening for the classic form began in 1977 in Alaska and is now in place in all 50 states in the United States and in more than 40 countries.[5,6] On the basis of data from millions of newborns screened worldwide, classic CAH occurs in 1 in 10,000 to 1 in 20,000 live births.[7,8] Nonclassic CAH was first identified in 1957 by French biochemist Jacques Decourt and colleagues,[9] and two decades later, studies of relatives of patients with classic CAH[10] revealed that some people with biochemical and genetic nonclassic CAH are asymptomatic and do not require therapy. Nonclassic CAH is common worldwide, with an estimated prevalence ranging from 1 case per 200 persons to 1 case per 1000 persons.[11]

Unlike the therapeutic approaches to other forms of adrenal insufficiency, therapeutic goals in CAH are twofold: first, to replace deficient hormones, and second, to reduce excessive androgen levels. Although the overwhelming majority of patients with CAH survive the disease, thanks to advances in genetics, metabolomics, and treatment strategies, existing therapies have failed to prevent multiple coexisting conditions, and deaths due to adrenal crisis still occur. This review summarizes the genetic and pathophysiological features of CAH, as well as current views regarding the diagnosis, treatment, and management of severe and mild forms of the disease.

GENETIC FEATURES

CYP21A2 maps to chromosome 6 (6p21.3), which is within the major histocompatibility complex at a locus of low copy repeats and includes active genes and pseu-

dogenes (Fig. 1A). More than 200 *CYP21A2* mutations are known; however, most mutations involve 10 deleterious sequences derived from the nonfunctional *CYP21A1P* and generated through misalignment and gene conversion during meiosis of homologous genes.[7,14] Approximately 20 to 30% of *CYP21A2* classic mutations are 30-kb deletions, usually associated with a null mutation.[15,16] However, the junction sites can be clinically relevant, in that approximately 3% of deletions retain partial 21-hydroxylase activity because of the location of the junction sites and are associated with a milder phenotype[17] (Fig. 1B). Most affected persons are compound heterozygotes with different mutations on each allele and a phenotype corresponding to the milder gene defect.

Approximately 10% of patients with CAH have CAH-X syndrome, which is characterized by features of CAH combined with features of the hypermobility-type Ehlers–Danlos syndrome and is due to a contiguous gene deletion that disrupts both *CYP21A2* and *TNXB*, diagnosed by genotyping.[18-20] *TNXB* encodes tenascin X, a large extracellular matrix protein that participates in collagen deposition.[21] The majority of CAH-X syndrome alleles are due to the monoallelic presence of a nonfunctional *TNXA/TNXB* chimeric gene; biallelic inheritance results in more severe symptomatology.[12] The clinical phenotype of CAH-X includes joint hypermobility, arthralgias, joint dislocations, hernias, and midline defects that can include cardiac structural abnormalities.[12,20]

Steroid hormone measurements are the standard for diagnosing CAH. Genotyping is not used as a first-line diagnostic test because of the complexity of the *CYP21A2* locus. Gene duplications and deletions, the *CYP21A1P* pseudogene, and multiple mutations in some alleles make it difficult to distinguish affected patients from carriers, and parental genotyping is often needed to confirm the genotype.

STEROIDOGENESIS

In the adrenal cortex, the fate of nascent pregnenolone derives from the relative expression of downstream enzymes (Fig. 2). Without 21-hydroxylase, cortisol precursors are shunted to produce androgen precursors.[23] Some 17-hydroxyprogesterone is metabolized to 21-deoxycortisol, which unlike 17-hydroxyprogesterone, is not produced in the gonads and is uniquely adrenal-derived. Hence, 21-deoxycortisol is a more specific biomarker of 21-hydroxylase deficiency than is 17-hydroxyprogesterone and has been incorporated into some newborn screening protocols.[24] Furthermore, androstenedione is an excellent substrate for 11-hydroxylase, which yields 11β-hydroxyandrostenedione, the most abundant androgen precursor in nearly all patients with 21-hydroxylase deficiency.[22] Extraadrenal metabolism converts 11β-hydroxyandrostenedione to the androgen 11-ketotestosterone,[22] which is a potent agonist of the androgen receptor[25] (Fig. 2). For additional information, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of CAH is classified as classic or nonclassic (Fig. 1C). The subdivision of classic CAH into salt-wasting and simple-virilizing forms, which is based on the capacity of the adrenal to produce small amounts of aldosterone in the simple-virilizing form, has fallen out of favor because all patients lose salt to some degree.[26] Clinical presentations overlap,[13] and this subtyping is often not clinically meaningful.

INFANCY

Most cases of CAH in infants are first detected by means of newborn screening, which has reduced morbidity and mortality and has led to less severe hyponatremia and shorter hospitalizations at diagnosis.[27,28] Protocols for detection vary but are mostly based on the presence of elevated 17-hydroxyprogesterone levels on immunoassay. However, 17-hydroxyprogesterone levels can also be elevated in healthy neonates during the first 1 to 2 days of life and in premature and ill neonates, posing a diagnostic challenge. False positive results due to physiological increases can often be identified through adjustment for gestational age, with or without consideration of birth weight.[5,29] The use of second-tier screening by means of liquid chromatography with tandem mass spectrometry,[30] measurement of 21-deoxycortisol,[24] or genetic testing[31] has been shown to improve accuracy.

The diagnosis of CAH is based on a 17-hydroxyprogesterone level above 1000 ng per deciliter, but most affected infants have levels well above 5000 ng per deciliter. Although random steroid

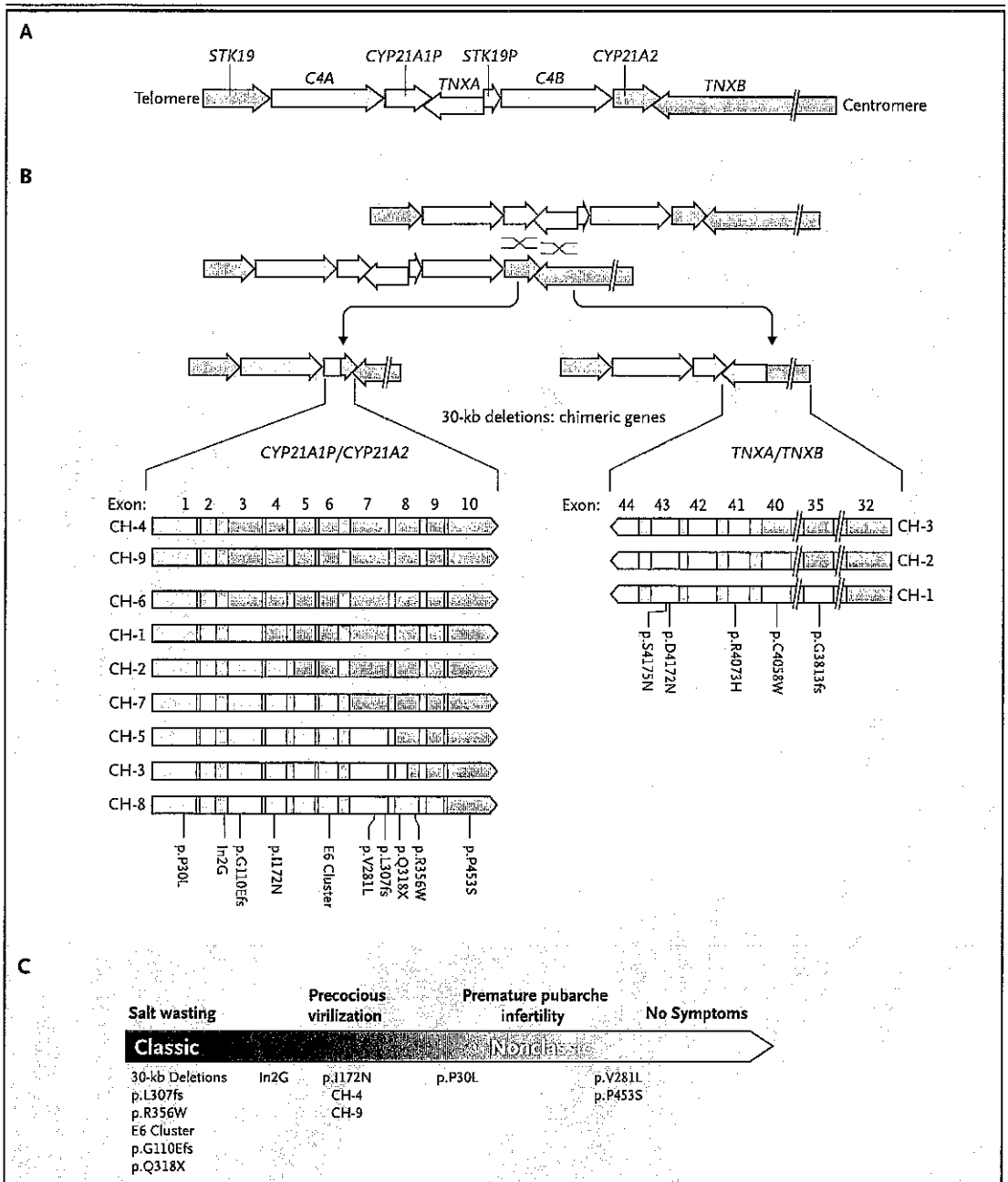

Figure 1. Genetic Features of Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (CAH).

In Panel A, the gene encoding 21-hydroxylase, *CYP21A2*, is arranged in tandem with a highly homologous *CYP21A1P* pseudogene, the complement component 4 genes (*C4A* and *C4B*), the tenascin X active gene (*TNXB*) and a truncated pseudogene (*TNXA*), and the serine–threonine nuclear protein kinase active gene (*RP1* [synonym, *STK19*]) and a truncated pseudogene (*RP2* [synonym, *STK19P*]). Arrows indicate transcriptional orientation. In Panel B, the orange X and the blue X denote unequal crossover between an active gene and a pseudogene during meiosis, which results in a 30-kb deletion and the formation of nonfunctional chimeric genes (*CYP21A1P/CYP21A2* or *TNXA/TNXB*). Approximately 20 to 30% of *CYP21A2* mutations are 30-kb deletions, and most of the nine *CYP21A1P/CYP21A2* chimeras encode null alleles; the exceptions are CH-4 and CH-9, which retain partial 21-hydroxylase activity because of the location of the junction sites upstream of In2G. The three types of *TNXA/TNXB* chimeras disrupt both *CYP21A2* and *TNXB*, and patients with one chimeric allele have hypermobility-type Ehlers–Danlos syndrome, called CAH-X syndrome.[12] In Panel C, the common mutations are shown in relation to the phenotypic spectrum, ranging from complete loss to about 30% of 21-hydroxylase activity. The correlation between genotype and phenotype for severe mutations (0 to 1% activity) is strong, and greater phenotypic variability is observed among intermediate and less-severe genotypes.[13]

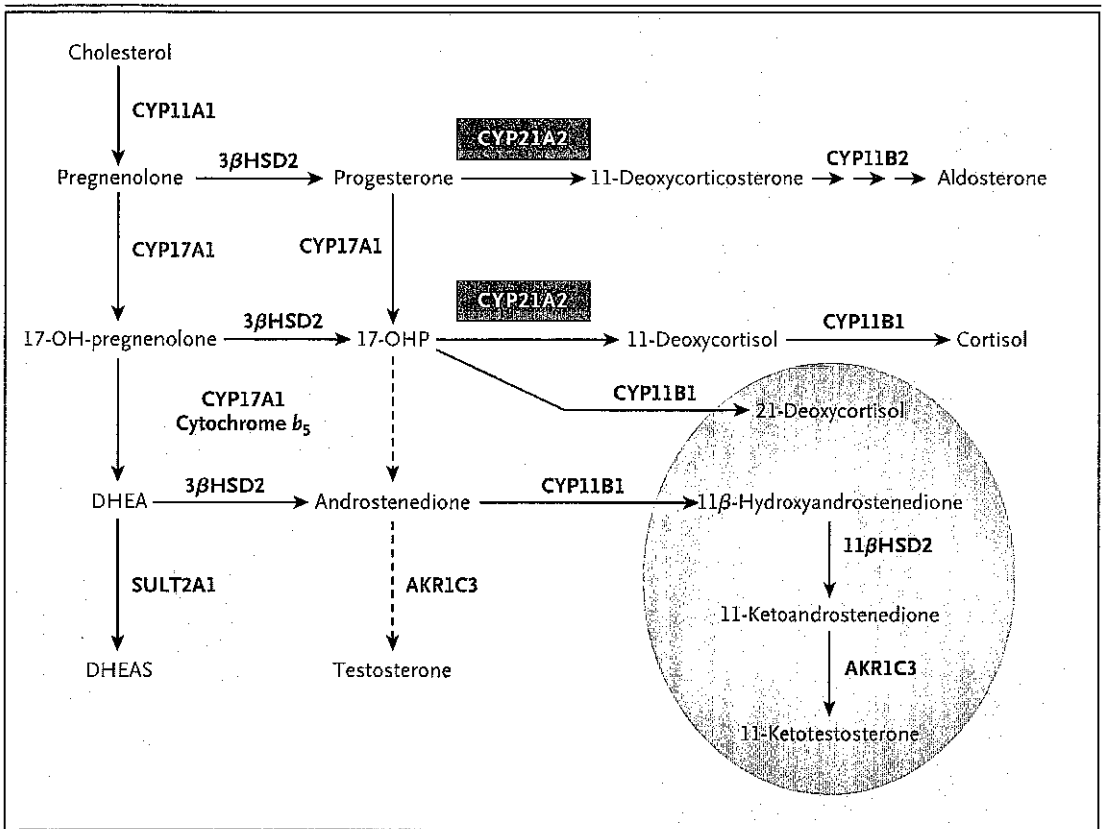

Figure 2. Pathways of Steroid Biosynthesis in the Adrenal Cortex.

All steroid synthesis starts with the conversion of cholesterol to pregnenolone through the cholesterol side-chain cleavage enzyme (CYP11A1). The 3β-hydroxysteroid dehydrogenase type 2 enzyme (3βHSD2) converts pregnenolone, 17-hydroxypregnenolone (17-OH-pregnenolone), and dehydroepiandrosterone (DHEA) to progesterone, 17-hydroxyprogesterone (17-OHP), and androstenedione, respectively. In the zona glomerulosa, 21-hydroxylase (CYP21A2) converts progesterone to 11-deoxycorticosterone, and aldosterone synthase (CYP11B2) catalyzes the three oxygenations required to convert 11-deoxycorticosterone to aldosterone. The adjacent zona fasciculata expresses the enzymes required for the orchestration of efficient cortisol production, including 17α-hydroxylase–17,20-lyase (CYP17A1, an enzyme with dual activities), which converts progesterone to 17-OHP. Ordinarily, 17-OHP is an excellent substrate for CYP21A2, yielding 11-deoxycortisol, and 11β-hydroxylase (CYP11B1) catalyzes the final oxygenation reaction to yield cortisol. Some of the 17-OHP that accumulates in 21-hydroxylase deficiency is converted through CYP11B1 to 21-deoxycortisol. In the inner zona reticularis, cytochrome b_5 activates the 17,20-lyase activity of CYP17A1 and allows DHEA synthesis, and the sulfotransferase SULT2A1 sulfonates DHEA to DHEA sulfate (DHEAS). Deficient CYP21A2 activity shunts cortisol precursors to androstenedione, and the adrenal produces some testosterone through AKR1C3. Much of the androstenedione is metabolized through CYP11B1 to 11β-hydroxyandrostenedione, which is converted primarily in peripheral tissues to 11-ketoandrostenedione through 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) and then to 11-ketotestosterone. These major adrenal-derived androgens and precursors in patients with CAH are shown,[22] with 21-deoxycortisol, in the shaded area.

measurements may be informative, a corticotropin stimulation test is recommended to confirm the diagnosis and rule out more rare disorders of steroidogenesis.[6,7] Elevation of 17-hydroxyprogesterone levels may occur with 11β-hydroxylase deficiency but also with 3β-hydroxysteroid dehydrogenase deficiency and cytochrome P-450 oxidoreductase deficiency; the forms are distinguished by measuring several steroids with corticotropin stimulation testing (Table 1).[7]

The clinical presentation differs according to sex (Table 1). In classic CAH, high levels of adrenal-derived androgens affect the development of the external genitalia in 46,XX fetuses, beginning in the first trimester. Clitoral enlargement, partially fused labia majora, and a urogenital sinus in place of separate urethral and vaginal openings are commonly found. The uterus, fallopian tubes, and ovaries are formed normally. Excess adrenal androgens do not affect 46,XY sexual differentiation.

Table 1. Diagnosis and Treatment of Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (CAH) According to Age.*

Approach	Infancy	Childhood	Adolescence and Adulthood
Diagnosis			
Symptoms and signs at presentation	Positive newborn screen, atypical genitalia (46,XX), poor feeding, weight loss, dehydration with low sodium, high potassium	Increased growth velocity, precocious pubarche†, early-onset adult apocrine odor	Hirsutism, oligomenorrhea, subfertility
Hormonal findings	Increased 17-OHP and androstenedione, decreased cortisol (in classic CAH) Corticotropin (cosyntropin) stimulation: 17-OHP >1000 ng/dl (30 nmol/liter), usually >5000 ng/dl (150 nmol/liter) in classic CAH Rule out other rare disorders of steroidogenesis‡	Same as for infancy	Corticotropin (cosyntropin) stimulation: 17-OHP >1000 ng/dl (30 nmol/liter) In nonclassic CAH, cortisol normal or near normal
Additional considerations	Pelvic ultrasonography to determine presence or absence of uterus in cases of atypical genitalia Measurement of electrolytes to evaluate sodium and potassium homeostasis Stimulation test may be delayed in sick infants	Radiographic assessment of bone age (left hand) to assess for skeletal maturation Distinguish classic from nonclassic CAH on the basis of cortisol values and disease severity	Early-morning, follicular-phase 17-OHP <200 ng/dl (6 nmol/liter) often rules out nonclassic CAH Genotyping and genetic counseling before pregnancy
Treatment			
At diagnosis	Treatment initiated after testing and before results are available, to prevent adrenal crisis	Treatment indicated for classic CAH and symptomatic nonclassic CAH	Treatment indicated for symptomatic nonclassic CAH
Long-term therapy	Hydrocortisone three times daily (10–18 mg/m^2/day) Fludrocortisone (50–200 μg) once or twice daily Sodium chloride, 1 to 2 g (17 to 34 mmol/liter) per day, divided into several feedings, in first year	Classic CAH: hydrocortisone three times daily (10–18 mg/m^2/day); fludrocortisone (50–200 μg) once or twice daily Nonclassic CAH: hydrocortisone three times daily (8–12 mg/m^2/day)	Classic CAH: may use hydrocortisone (approximately 15–40 mg/day), long-acting glucocorticoid§, or both; continue fludrocortisone Nonclassic CAH: hydrocortisone twice or three times daily, or prednisone or prednisolone, generally ≤4 mg/day
Stress dosing for prevention of adrenal crisis	For febrile illnesses, 2–3 times usual daily dose of glucocorticoid divided into 4 doses given every 6 hr Increased fluid intake and frequent ingestion of simple and complex carbohydrates Intramuscular injection of hydrocortisone, 50–100 mg/m^2, if oral intake not possible; activate emergency services after injection	For febrile illnesses, 2–3 times usual daily dose of glucocorticoid, divided into 4 doses given every 6 hr Increased fluid intake and frequent ingestion of simple and complex carbohydrates Intramuscular injection of hydrocortisone, 50–100 mg/m^2, if oral intake not possible; activate emergency services after injection	For febrile illnesses, 2–3 times usual daily dose of glucocorticoid divided into 3 doses Increased fluid intake and frequent ingestion of simple and complex carbohydrates Intramuscular injection of hydrocortisone, 100 mg, if oral intake not possible; activate emergency services after injection

Emergency therapy¶	Hydrocortisone, 50–100 mg/m^2 (neonatal dose, 25 mg), given as IV (or intramuscular) bolus, followed by hydrocortisone, 50–100 mg/m^2 per day, divided, every 6 hr Parenteral bolus of normal (0.9%) saline, 20 ml/kg; repeated, additional fluids as clinically indicated IV bolus of dextrose, 0.5–1 g/kg, as needed for hypoglycemia	Hydrocortisone, 50–100 mg/m^2 (maximum dose, 100 mg), given as IV (or intramuscular) bolus, followed by hydrocortisone, 50–100 mg/m^2 per day, divided, every 6 hr Parenteral bolus of normal (0.9%) saline, 20 ml/kg; repeated, additional fluids as clinically indicated IV bolus of dextrose, 0.5–1 g/kg, as needed for hypoglycemia	Hydrocortisone, 100 mg, given as IV (or intramuscular) bolus, followed by hydrocortisone, 200 mg per day, divided, every 6 hr Parenteral bolus of normal (0.9%) saline, 500–1000 ml; repeated, additional fluids as clinically indicated IV bolus of dextrose, 0.5–1 g/kg, as needed for hypoglycemia
Additional considerations	Therapeutic plan for atypical genitalia should involve interdisciplinary team Increased renal sensitivity to mineralocorticoid at around 6 mo requires reduction of fludrocortisone dose Risk of hypoglycemia with illnesses	GnRH analogue may be needed for central precocious puberty‖ Children with classic CAH at risk for hypoglycemia with illnesses May need additional salt intake during hot summer months or on days of sports activities Healthy lifestyle counseling plus age-appropriate vitamin D and calcium intake recommended Patients with nonclassic CAH who are not receiving glucocorticoid therapy do not need stress dose of steroids	Patients treated for nonclassic CAH during childhood may not need therapy as adults Adolescent boys with nonclassic CAH can be weaned off treatment in midpuberty Bone mineral density and testicular adrenal rest screening during young adulthood Girls and women of reproductive age who are heterosexually active should not be treated with dexamethasone Genetic studies recommended for reproductive planning Glucocorticoid dose should be increased in third trimester for pregnant patients with classic CAH May need additional salt intake during hot summer months or on days of sports activities Healthy lifestyle counseling plus age-appropriate vitamin D and calcium intake recommended Patients with nonclassic CAH who are not receiving glucocorticoid therapy do not need stress dose of steroids

* GnRH denotes gonadotropin-releasing hormone, IV intravenous, and 17-OHP 17-hydroxyprogesterone.
† Precocious pubarche is defined as the presence of pubic hair before 8 years of age in girls and 9 years of age in boys.
‡ Measure 17-OHP, cortisol, 11-deoxycortisol, 17-hydroxypregnenolone, dehydroepiandrosterone, and androstenedione.
§ May use long-acting glucocorticoid with caution when growth is complete. To calculate daily doses, divide the hydrocortisone dose by 5 for prednisone and prednisolone, and by 80 for dexamethasone. Essential hypertension is treated with conventional agents such as calcium-channel antagonists, and fludrocortisone is continued.
¶ Fludrocortisone is not given.
‖ Central precocious puberty, due to maturation of the hypothalamic–pituitary–gonadal axis, is defined as the onset of puberty before 8 years of age in girls and 9 years of age in boys.

Approximately 75% of infants with classic CAH have a salt-wasting adrenal crisis within the first 3 weeks after birth that is life-threatening if the disorder is not diagnosed and treated. In the most severe form, lack of in utero production of cortisol affects the development of the adrenal medulla, resulting in epinephrine deficiency.[32] The combination of cortisol, epinephrine, and aldosterone deficiencies results in hypovolemia, hyponatremia, and hyperkalemia, which, if undiagnosed, lead to eventual shock and hypoglycemia. Given these problems, the diagnosis of CAH should be considered in infants who present with poor weight gain, poor feeding, and dehydration with hyponatremia and hyperkalemia.

CHILDHOOD

In approximately 25% of patients with classic CAH, aldosterone production is sufficient to maintain sodium balance in early childhood. In the absence of newborn screening, affected children will present with signs of androgen excess, such as pubic hair and accelerated linear growth velocity, typically before the age of 4 years,[33] and girls may have clitoromegaly or a urogenital sinus that was not noticed earlier in life.

The diagnostic criterion for classic CAH in childhood is the same as the criterion in infancy. A basal or corticotropin-stimulated 17-hydroxyprogesterone level above 1000 ng per deciliter establishes the diagnosis. Children with nonclassic CAH may have evidence of androgen excess at various ages, but they are older and less symptomatic than children with classic CAH presenting beyond the neonatal period, and girls have normal genitalia.

ADOLESCENCE AND ADULTHOOD

The mild hyperandrogenism associated with nonclassic CAH can develop in adolescence or adulthood in affected females but is asymptomatic in postpubertal males. Symptoms may include hirsutism, acne, menstrual dysfunction, subfertility, and recurrent miscarriages, but there may be no symptoms at all. The clinical features are difficult to differentiate from the more common polycystic ovary syndrome, and steroid testing is needed to establish the diagnosis. Measurement of 17-hydroxyprogesterone levels may be performed in the morning of the menstrual follicular phase to reduce the possibility of false positive results[7]; however, a corticotropin stimulation test is usually required to establish the diagnosis.

IMPLICATIONS OF ADVERSE OUTCOMES ON CLINICAL PRACTICE

Most of the adverse outcomes in patients with classic CAH are attributable to cortisol deficiency and the challenge of replacing glucocorticoids in order to suppress the corticotropin-driven androgen excess adequately while avoiding excessive glucocorticoid exposure. Adverse outcomes may occur throughout the patient's lifetime because of the multitude of hormonal imbalances (Fig. 3).

ADRENAL CRISIS AND INCREASED MORTALITY

Despite the reduction in infant mortality as a result of neonatal screening for CAH,[34] patients of all ages are at risk for death from adrenal crises, which are most often triggered by infectious illnesses. Adrenal crisis was reported as the leading cause of death in 588 patients with CAH in a Swedish nationwide study,[35] and in a retrospective, matched-cohort study in the United Kingdom, all-cause mortality rates were more than 5 times as high among patients with CAH as among controls.[36] Gastrointestinal illnesses are a common precipitant of adrenal crises throughout life in patients with CAH.[37,38] Life-threatening hypoglycemia, sometimes with seizures but rarely reported to result in permanent neurologic sequelae, can occur with adrenal crisis, especially in children.[38] Rapid clinical deterioration and adverse outcomes are related more to hypoglycemia than to electrolyte disturbances.[39,40] Accordingly, stress dosing during illness should include increases in the dose of glucocorticoids and in the frequency of administration, with frequent intake of simple and complex carbohydrates (Table 1).[38] Although patients with nonclassic CAH commonly have mild but clinically silent cortisol impairment,[41] adrenal crisis in nonclassic CAH has been reported only in the context of glucocorticoid therapy, as a result of secondary iatrogenic suppression of the hypothalamic–pituitary–adrenal axis.[38]

GENITAL ATYPIA

The common practice of performing genital surgery in the first year of life for atypical genitalia in infants with 46,XX CAH has become increas-

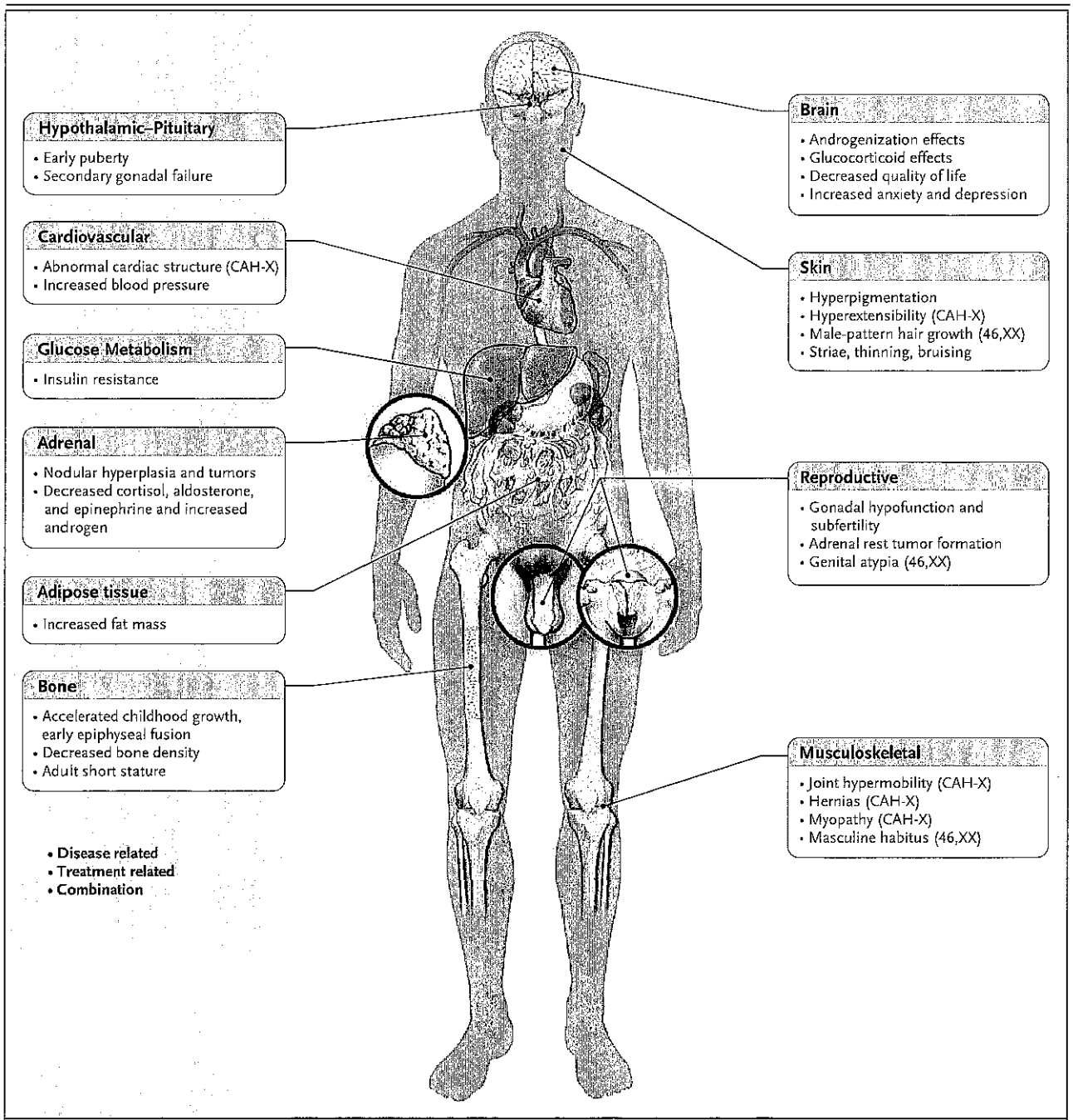

Figure 3. Disease-Related and Treatment-Related Features of CAH.

Disease-related manifestations are shown in blue, treatment-related manifestations are shown in red, and clinical manifestations related to both the disease and the treatment are shown in brown. CAH-X syndrome is characterized by features of CAH combined with features of the hypermobility-type Ehlers–Danlos syndrome.

ingly controversial. Vaginoplasty and urogenital sinus division allow for intromission and the potential for fertility, but concerns have emerged regarding sexual-function outcomes and consideration of a possible male sexual identity, especially in fully virilized 46,XX infants.[42] The clinical practice guideline from the Endocrine Society and a European expert consensus statement rec-

ommend that parents be informed about surgical options, including delayed surgery and observation until the child is older and can participate in decision making.[7,43] If surgery is deferred, an examination to determine whether the anatomy allows for adequate menstrual flow is needed before puberty for female patients. Testosterone therapy would be indicated for pubertal induction if an affected girl has a male sexual identity. Prenatal dexamethasone treatment reduces virilization of the external genitalia in 46,XX-affected fetuses, but it is no longer recommended because of unknown safety and potential effects on the developing fetal brain.[7] Long-term data on outcomes in persons who have undergone surgery and those who have not are needed.

IMPAIRED GROWTH AND DEVELOPMENT

Short stature in adulthood is a consequence of both hyperandrogenism and glucocorticoid treatment in patients with CAH. Long-term glucocorticoid administration suppresses growth, and elevated circulating levels of adrenal sex steroids accelerate skeletal maturation and may trigger an early onset of central puberty. A meta-analysis of studies involving patients treated for CAH showed a mean adult height score of −1.4 SD (10 cm) below the population mean.[44] The meta-analysis also showed that mineralocorticoid use during childhood was associated with increased height as compared with no mineralocorticoid use, since mineralocorticoid replacement ensures euvolemia, which diminishes corticotropin stimulation and subsequent adrenal androgen synthesis. The growth-suppressing effect of glucocorticoids is especially apparent during infancy and puberty, and doses exceeding 15 to 20 mg per square meter of body-surface area per day during these developmental periods decrease final adult height.[45,46] Patients with nonclassic CAH may also have compromised adult height, but the deficit is less severe than in patients with the classic form.[33] Although long-acting glucocorticoids are effective in suppressing adrenal androgens, these drugs are more likely than short-acting hydrocortisone to impede growth velocity and are not recommended for long-term treatment in children.

PSYCHOLOGICAL ASPECTS AND BRAIN EFFECTS

Data on the psychological aspects and brain effects of CAH are limited. Altered fetal and postnatal exposure to androgens and glucocorticoids in patients with CAH influences brain development and function, possibly affecting mental health. Registry and cohort studies have shown a higher prevalence of anxiety, depression, alcohol misuse, personality disorders, and suicidality among male patients and adjustment disorders among female patients with classic CAH than among controls.[36,47,48] Substance abuse and attention deficit–hyperactivity disorder have been reported among some women with the most severe null genotype[47] and among some boys and men who receive a diagnosis after the neonatal period.[48,49] As compared with unaffected girls, those with classic CAH have been reported to have more aggressive behavior[50] but improved spatial navigation abilities,[51] and patterns of amygdala activation differ between affected and unaffected girls.[52]

Glucocorticoid therapy in CAH has been reported to affect working memory and result in brain changes, including white-matter hyperintensities that suggest a reduction in the structural integrity of white matter.[53] Cognitive impairment, if present, has sometimes been thought to be related to hypoglycemia and salt loss at the initial presentation.[54]

Sexual orientation in women with CAH has been reported to correlate with androgen exposure, with the prevalence of a female sexual orientation ranging from approximately 5 to 15% among affected women.[55] Avoidance of romantic relationships is common. Although hormonal influences may contribute to such behavior, women with classic CAH have reported stigma in reaction to atypical genital and nongenital sexual characteristics of CAH, contributing to avoidance of intimacy.[56]

The reported quality of life for patients with CAH varies, possibly because of differences in health care provision and treatment regimens among countries; in addition, increased impairment in the quality of life has been observed in patients with the more severe forms of CAH.[7,57] Challenges allegedly vary according to sex, but all patients are subject to the emotional stress of living with a chronic disease, and many have weight and height disturbances and are at risk for infertility.

Patients with nonclassic CAH have less pronounced hormonal disturbances and have not been extensively studied. However, alterations in the hypothalamic–pituitary–adrenal axis are pres-

ent even in this mild form of the disease and might contribute to psychiatric vulnerability.

SUBFERTILITY

The challenges to conception that women with classic CAH face include anatomical impediments, hormonal disturbances, and psychological effects of the condition. Labioscrotal fusion and the presence of a urogenital sinus preclude vaginal intercourse unless reconstructive surgery is performed, and subsequent vaginal stenosis may cause dyspareunia.[58] Although elevated adrenal-derived androgen levels, oligo-ovulation or anovulation, and secondary polycystic ovaries can impair fertility, the greatest hormonal obstacle to fertility is elevated production of adrenal-derived progesterone. Progesterone accumulation upstream of 17-hydroxyprogesterone during the follicular phase thins the endometrial lining and alters cervical mucous in a manner similar to the action of progestin contraceptives and also leads to oligomenorrhea or amenorrhea. Strict hormonal control for conception can require glucocorticoid intensification beyond that which would otherwise constitute adequate control.[59]

Preconception genetic counseling is advised, since the carrier frequency for a classic CAH allele is about 1 in 60. Consequently, without partner genotyping, the risk of having a child affected with classic CAH is 1 in 120. The majority of people who receive a diagnosis of nonclassic CAH carry a mutation associated with the classic form. Theoretically, the chance that a patient with nonclassic CAH will have a child with classic CAH is 1 in 250, but this risk was reported to be 1 to 2% in two large cohort studies.[60,61]

Nonclassic CAH is sometimes diagnosed during an evaluation for oligomenorrhea or amenorrhea and infertility. However, an estimated 90% of women with nonclassic CAH never receive a diagnosis. Once they start trying to conceive, roughly 83% of women with known nonclassic CAH become pregnant within 1 year, with or without glucocorticoid therapy. Such women have consistently been found to be at increased risk for miscarriage. In two large retrospective studies, the miscarriage risk was about 25% without therapy and less than 10% with hydrocortisone treatment.[60,61]

Many men with classic CAH have oligospermia or azoospermia for at least two reasons. First, elevated adrenal-derived androgen levels provide negative feedback to the hypothalamic–pituitary–testicular axis, suppress both gonadotropin secretion and testosterone synthesis from Leydig cells, and prevent spermatogenesis. Second, testicular adrenal rest tumors (TARTs) develop in 30 to 50% of adolescent boys and men with classic CAH, particularly after periods of poor control or nonadherence to treatment.[33] TARTs are usually bilateral and arise from the rete testis. The tumors are easily identified with ultrasonography, which should be performed on completion of puberty in boys with classic CAH. TARTs can cause irreversible damage to the Sertoli cells and developing germ cells. The presence of a TART and elevated follicle-stimulating hormone levels are poor prognostic factors for male fertility.[62] If a TART is identified, ultrasound examinations should be performed at least annually, depending on the size of the tumor, laboratory and physical examination findings, and the patient's wishes with respect to the pursuit of fertility. Chronic loss of negative feedback and elevated corticotropin levels can lead to adrenal enlargement, nodule formation, and zonal disruption. Serum 11-oxyandrogen levels correlate directly with adrenal size and the presence or absence of a TART, demonstrating their use as biomarkers of long-term disease control.[63]

Adrenal myelolipomas, which are commonly bilateral though asymmetric, are also characteristic tumors in patients with classic CAH, but the pathogenesis of these tumors is unknown.[64] Although benign and not steroid-producing, adrenal myelolipomas tend to grow to massive size, even if glucocorticoid treatment is intensified, and may require surgical removal because of mass effects.

In women with classic CAH, adrenal rest tumors can develop in the ovaries or adjacent uterine ligaments. These tumors are not usually identified by means of conventional imaging.

COEXISTING METABOLIC CONDITIONS

In patients with classic CAH, the development of metabolic consequences from chronic exposure to supraphysiologic glucocorticoid therapy is likely, yet the anabolic actions of androgens may mitigate some of the effects of glucocorticoids. A meta-analysis of 20 studies that focused on cardiovascular risk factors in glucocorticoid-treated patients with CAH identified small increases in carotid intima–media thickness and

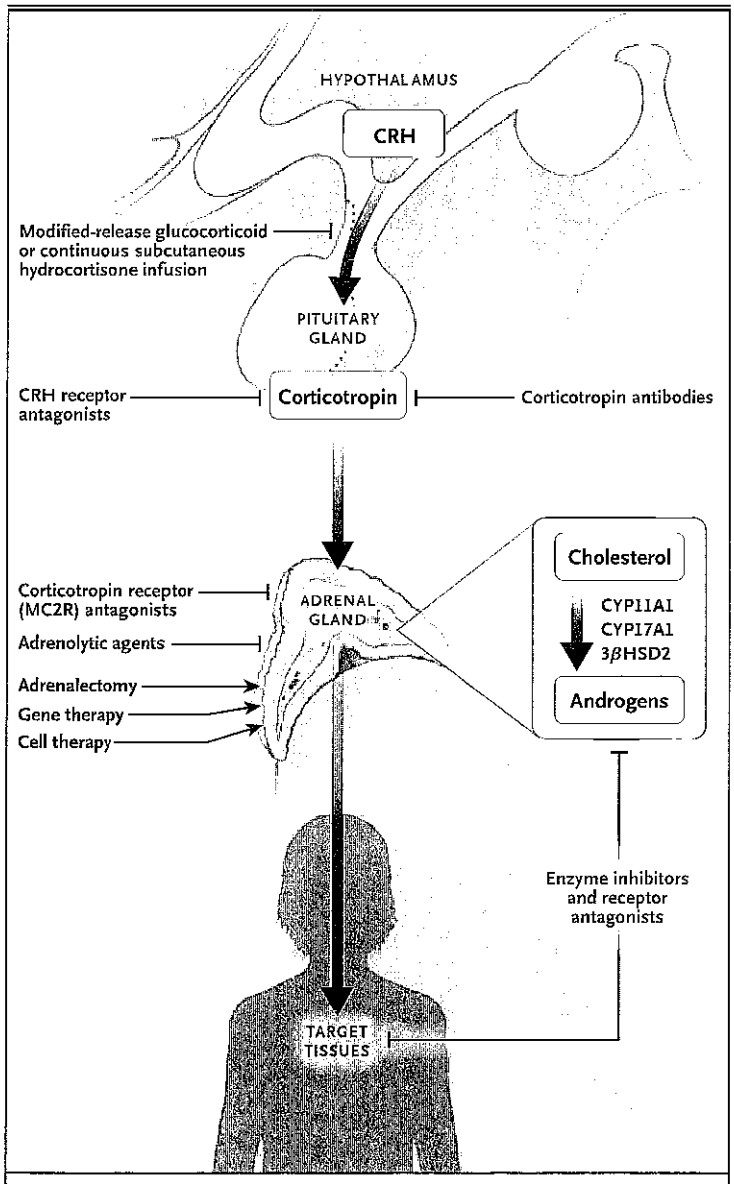

Figure 4. New Therapies for CAH.

New therapeutic approaches target various aspects of the pathophysiology of CAH. Circadian cortisol replacement through the use of a modified-release glucocorticoid or subcutaneous hydrocortisone infusion is intended to control corticotropin-driven hyperandrogenism by replacing cortisol in a physiologic manner.[70,71] Other approaches to reducing androgen production without the need for long-term supraphysiologic glucocorticoid exposure include administration of corticotropin-releasing factor receptor 1 antagonists, corticotropin antibodies, corticotropin receptor (melanocortin 2 receptor [MC2R]) antagonists, or adrenolytic agents; adrenalectomy; and pharmacologic inhibition of steroidogenic enzymes or steroid receptors in the adrenal or peripheral tissues.[72-76] Since CAH is a monogenic disorder, gene therapy with cell-based and gene-editing technologies may restore defective steroidogenesis (see additional information in the Supplementary Appendix). CRH denotes corticotropin-releasing hormone (sometimes referred to as corticotropin-releasing factor [CRF]).

insulin resistance, as compared with healthy controls, as well as a higher prevalence of hypertension, hyperlipidemia, atrial fibrillation, venous thromboembolism, obesity, and diabetes.[65] Because most patients studied are less than 50 years of age, data on cardiovascular events are insufficient to ascribe risk. Nevertheless, a Swedish national cohort study showed an increased incidence of cardiovascular and metabolic disorders among adults with classic CAH.[66] Furthermore, women with classic CAH, as compared with age-matched controls, have been reported to have an increased risk of gestational diabetes, which is a known risk factor for the subsequent development of diabetes.[67] The Endocrine Society clinical practice guideline recommends early attention to cardiometabolic risk factors and counseling about healthy lifestyle choices.[7]

MANAGEMENT

Throughout the life span, the primary goal of therapy for each patient is to replace the adrenal insufficiency of CAH in order to maintain normal plasma volume and physiological balance. Thus, patients should be provided with detailed information about stress glucocorticoid dosing, medical alert identification, and emergency use of hydrocortisone injection. In children with CAH, an additional major goal of therapy is to suppress adrenal-derived androgen production sufficiently to allow for normal growth and development and achievement of normal adult height.

During the transition to care in adulthood, after linear growth has stopped, control of adrenal-derived androgen excess is often relaxed somewhat in order to limit exposure to prolonged glucocorticoid excess, since approximately 40% of adults with CAH are reported to have osteopenia.[33,68] Additional goals of care in adulthood are preservation of fertility and monitoring for long-term consequences of glucocorticoid therapy. Divided doses of hydrocortisone may be continued indefinitely or changed to a single dose of longer-acting synthetic glucocorticoid to increase adherence, but the latter is associated with a greater risk of iatrogenic Cushing's syndrome. When potent synthetic glucocorticoids are used, the dose should be carefully adjusted to provide the minimum amount required in order to achieve the desired control rather than arbitrarily determined according to available tablet sizes.

For women with nonclassic CAH, an oral contraceptive pill and spironolactone or cyproterone acetate, if available, are alternatives to glucocorticoids for managing hirsutism, acne, or both resulting from androgen excess. For men with nonclassic CAH, there is no medical indication for glucocorticoids except in the rare case in which the phenotype straddles the classic–nonclassic boundary, with a risk of infertility. Consequently, for boys, treatment is tapered in childhood and discontinued during adolescence.

When a woman with classic CAH attempts to conceive, adrenal-derived progesterone must be suppressed, with a goal of less than 0.6 ng per milliliter (2.0 nmol per liter). Dexamethasone is contraindicated during pregnancy because it is not metabolized by the placenta and therefore reaches the fetus. Treatment with hydrocortisone, prednisolone, or both, administered in two or three divided doses, was associated with successful pregnancies in 21 women with classic CAH, often with the use of 1 to 2 mg of prednisolone at bedtime.[59] For women with nonclassic CAH, treatment with 15 to 20 mg of hydrocortisone daily, started before conception and continued until term, is empirically associated with reduced rates of miscarriage.[61]

Men and adolescent boys with TARTs require glucocorticoid dosage intensification to achieve tumor shrinkage; however, TARTs develop fibrotic elements over time, which do not regress in response to glucocorticoids. Dexamethasone, administered twice daily, is often necessary to achieve the degree of corticotropin suppression necessary to shrink TARTs, relieve gonadotropin suppression, and allow recovery of testicular function and spermatogenesis. Large, confluent TARTs can be removed surgically, which will also eliminate the associated mass effect, but testicular testosterone and sperm production rarely return to normal levels.[69]

WHAT LIES AHEAD

Given the adverse consequences of chronic supraphysiologic glucocorticoid exposure, several alternative treatments based on the pathophysiology of CAH can be proposed, including diurnal cortisol replacement[70,71] and drugs that lower androgen levels and allow reduced glucocorticoid dosing (Fig. 4, with additional details provided in the Supplementary Appendix).[72-76] Some of these concepts have been tested in small trials, but none are currently approved by the Food and Drug Administration.

CONCLUSIONS

CAH is a complex and often life-threatening disease with a multitude of hormonal imbalances that can result in disease- and treatment-related adverse outcomes. Decades of progress have expanded our understanding of the pathophysiology, genetics, and manifestations of the disease, but additional advances are needed to improve therapy and outcomes.

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