Congenital Adrenal Hyperplasia

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PRACTICE GAPS

It is essential for pediatricians to know the spectrum of symptoms of congenital adrenal hyperplasia across different ages, including premature adrenarche, to properly identify the condition. General pediatricians can then work with pediatric endocrinologists for diagnostic testing and treatment of the patient.

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

1. Describe the underlying pathophysiology of congenital adrenal hyperplasia (CAH).
2. Identify common genetics associated with CAH.
3. List the different screening methods for detection of CAH.
4. Discuss the utility of cosyntropin stimulation testing in CAH.
5. Describe presenting clinical features of CAH at different stages of life.
6. Identify current therapies for CAH.
7. Discuss the need for stress dosing with additional glucocorticoids in patients with CAH.
8. List long-term effects of having CAH.

ABSTRACT

We describe congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, which is the most common primary adrenal insufficiency in children and adolescents. In this comprehensive review of CAH, we describe presentations at different life stages depending on disease severity. CAH is characterized by androgen excess secondary to impaired steroidogenesis in the adrenal glands. Diagnosis of CAH is most common during infancy with elevated 17-hydroxyprogesterone levels on the newborn screen in the United States. However, CAH can also present in childhood, with late-onset symptoms such as premature adrenarche, growth acceleration, hirsutism, and irregular menses. The growing child with CAH is treated with hydrocortisone for glucocorticoid replacement,

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ABBREVIATIONS

ART	adrenal rest tumor
BMD	bone mineral density
CAH	congenital adrenal hyperplasia
CRF1R	corticotropin-releasing factor type 1 receptor
MC2R	melanocortin-2 receptor
SV	simple virilizing
SW	salt-wasting
17-OHP	17-hydroxyprogesterone
3β-HSD	3β-hydroxysteroid dehydrogenase

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along with increased stress doses for acute illness, trauma, and procedures. Mineralocorticoid and salt replacement may also be necessary. Although 21-hydroxylase deficiency is the most common type of CAH, there are other rare types, such as 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiency. In addition, classic CAH is associated with long-term comorbidities, including cardiometabolic risk factors, impaired cognitive function, adrenal rest tumors, and bone health effects. Overall, early identification and treatment of CAH is important for the pediatric patient.

BACKGROUND

Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the most common cause of primary adrenal insufficiency in children. 21-Hydroxylase is a key enzyme in the steroidogenic biosynthesis pathway that converts cholesterol into cortisol and aldosterone in the adrenal cortex (Fig 1). Cortisol is an important hormone that increases glucose in the bloodstream while enhancing the utilization of glucose by the brain, regulates metabolism, and manages the immune response. Decreased cortisol production inherent in patients with CAH is partnered with a subsequent increase in corticotropin secretion from the pituitary gland. This increase in corticotropin secretion results in the accumulation of biosynthetic steroid precursor molecules proximal to the formation of 21-hydroxylase, such as 17-hydroxyprogesterone (17-OHP). These steroid precursors in excess are then shunted toward the androgen biosynthesis pathway in the adrenal gland, resulting in hyperandrogenism. In addition, recent studies have shown that patients with CAH have low levels of epinephrine circulation in response to stress, suggesting the presence of adrenal medulla dysfunction in CAH disease pathology. (1)

There are several forms of CAH due to 21-hydroxylase deficiency: severe, classic CAH that is either salt-wasting (SW) or simple virilizing (SV) (Fig 2), as well as mild, nonclassic CAH. Severity of CAH can be directly attributed to the level of enzyme functionality in each form. SW CAH has less than 1% residual enzyme activity, SV CAH has approximately 1% to 3%, and the mild, nonclassic form of CAH has 20% to 60%. (2)(3)(4) There is an overall frequency of classic CAH of 1 in 15,000 live births. (5)(6)(7) However, there is a much lower prevalence of classic CAH in Black and Asian populations. (8) The mild, nonclassic form of CAH has a higher prevalence overall, with 1 in 200 to 1,000 people affected, and an increased prevalence in individuals of Hispanic, Yugoslav, and Ashkenazi Jewish descent. (8)(9)

RARE TYPES OF CAH

Two rare types of enzyme deficiency that can result in CAH include 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency. 11β-Hydroxylase deficiency accounts for only approximately 5% to 8% of cases of CAH and affects the steroidogenic pathway after the 21-hydroxylase step, preventing the conversion of corticosterone to aldosterone, and 11-deoxycortisol to cortisol, in the adrenal cortex. This then results in an excess of androgens and a deficiency of both aldosterone and cortisol in the affected CAH population. However, patients do not require mineralocorticoid replacement due to the mineralocorticoid action of the steroid precursor deoxycorticosterone.

3β-HSD deficiency affects the pathway before the 21-hydroxylase step, affecting the conversion of pregnenolone to progesterone, and 17-hydroxypregnenolone to 17-OHP, resulting in cortisol and aldosterone deficiencies. 3β-HSD deficiency can impair androgen production (Fig 1). (10)(11)

11β-Hydroxylase deficiency affects approximately 1 in 100,000 to 200,000 live births. (12)(13) 3β-HSD deficiency is even less common, with the exact prevalence unknown but estimated to account for less than 1 in 1,000,000 births. (14)

CLINICAL PRESENTATION

Classic CAH typically presents during the newborn period when detected on newborn screening and/or by atypical genitalia in females. In the United States, classic CAH is commonly detected on state-mandated newborn screening by high levels of 17-OHP. Before the initiation of newborn screens, males with classic CAH would not be identified until they presented with signs of adrenal insufficiency, such as failure to thrive, poor feeding, dehydration, vomiting, diarrhea, hyperpigmentation, and abnormal electrolytes (eg, hyponatremia, hyperkalemia). These signs typically develop within the first 2 weeks after birth, with glucocorticoid and mineralocorticoid deficiencies precipitating an SW adrenal crisis. Females with classic CAH can be identified by varying degrees of external genitalia virilization (Fig 2). In very severe cases, female patients can be misidentified at birth as males. It is critical that pediatricians closely examine the newborn genitalia to determine the correct sex and should suspect that the patient could be a 46,XX female with CAH if there is a male with bilateral cryptorchidism.

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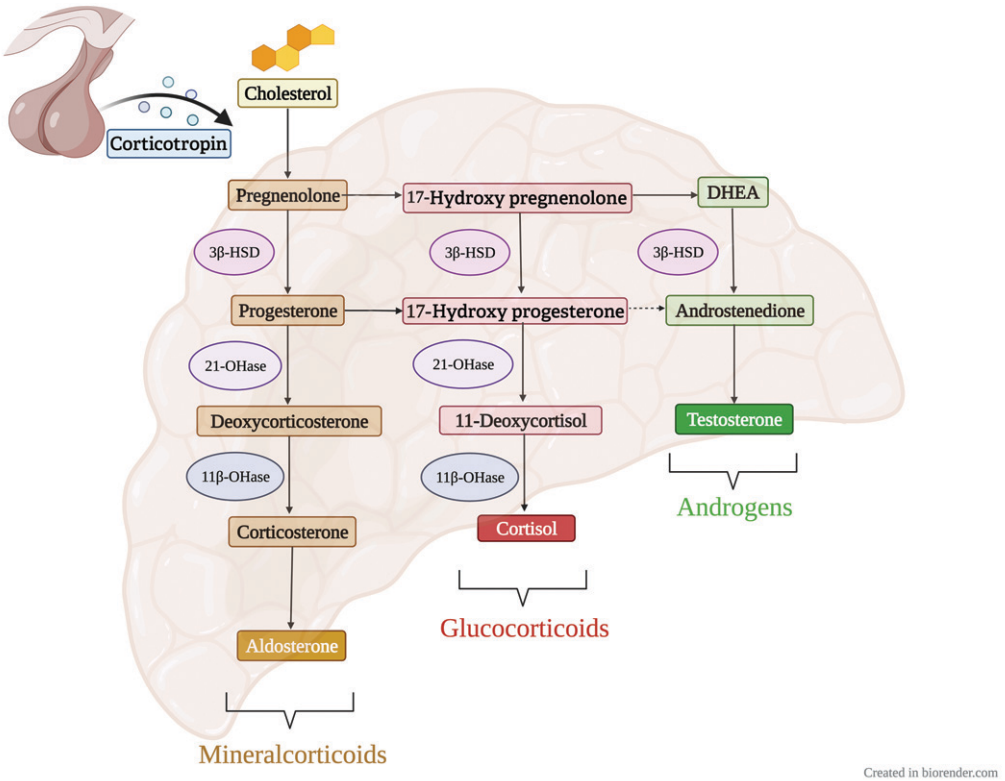

Figure 1. Steroidogenic biosynthesis pathway and enzyme deficiencies in congenital adrenal hyperplasia (CAH). Corticotropin from the pituitary gland stimulates the conversion of cholesterol into various steroid hormones in the adrenal gland. The steroidogenic pathway can be affected at different key steps depending on the type of enzyme deficiency: 21-hydroxylase (21-OHase) deficiency is the most common cause of CAH, and 11β-hydroxylase (11β-OHase) and 3β-hydroxysteroid dehydrogenase (3β-HSD) are more rare enzyme deficiencies resulting in CAH. DHEA=dehydroepiandrosterone.

Further karyotyping could then confirm the chromosomal sex of the newborn.

Patients with the mild, late-onset, nonclassic form of CAH will typically present later in childhood through adulthood. Patients with nonclassic CAH have a much wider spectrum of presentation based on virilization and age (Fig 3). Presentation at school-age typically includes signs of premature pubarche (eg, severe acne, axillary

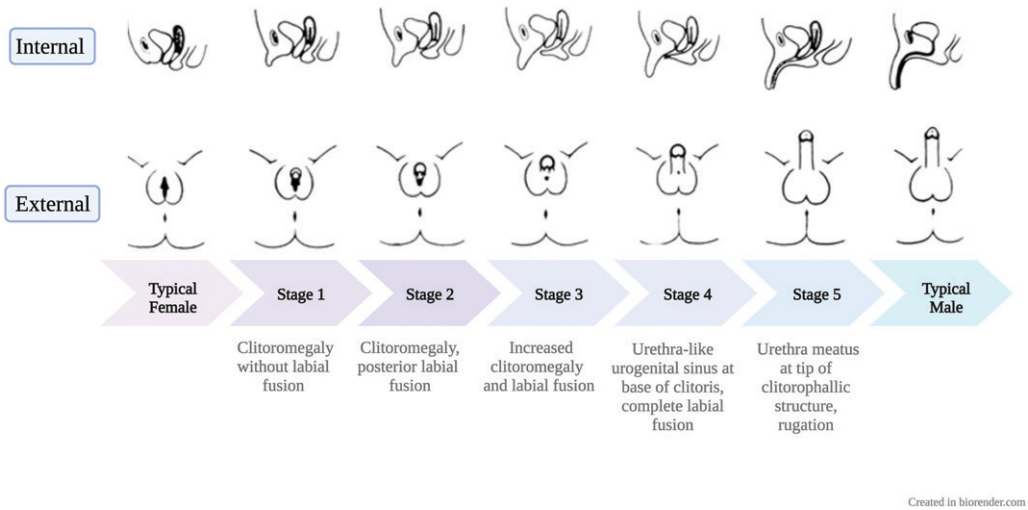

Figure 2. Prader scale of virilization of external female genitalia. From left to right, typical female external genital to increasingly virilized genitalia. Adapted from Yau et al. (70)

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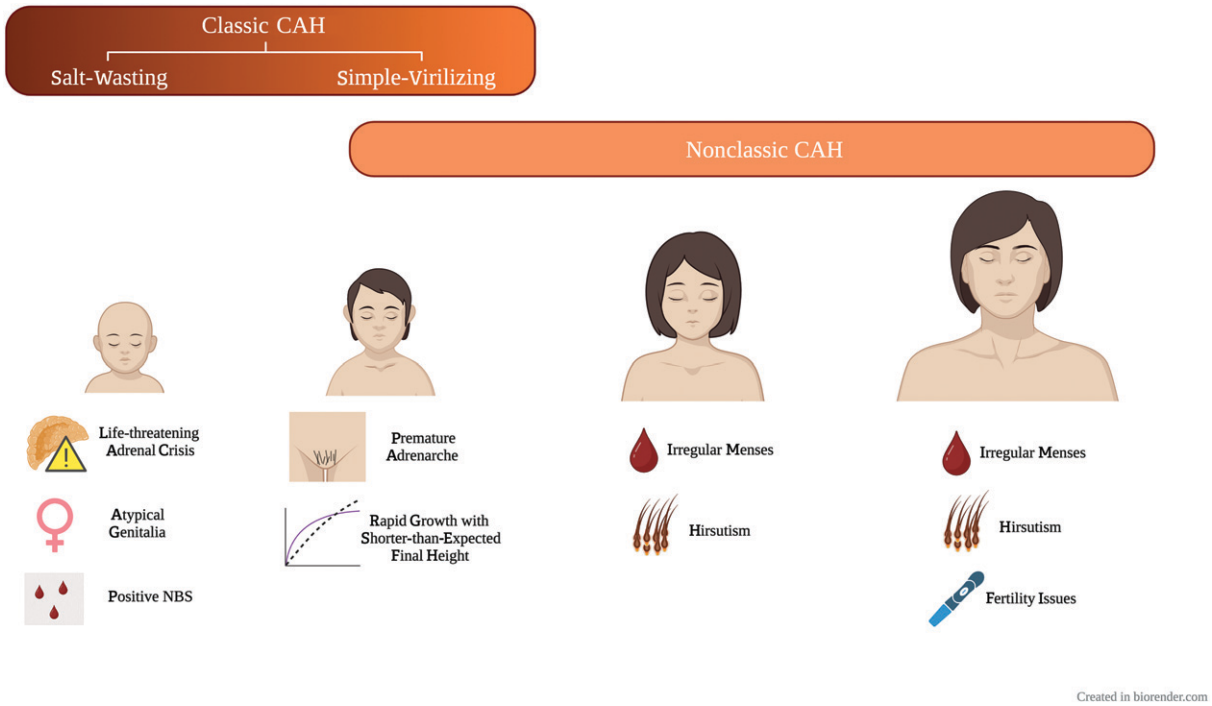

Figure 3. Typical presentations of patients with classic and nonclassic congenital adrenal hyperplasia (CAH) from birth to adulthood. From left to right are the common presentations of CAH during a patient's lifetime: birth, childhood, adolescence, and adulthood. CAH has 3 different forms of severity, with salt-wasting classic CAH being the most severe form and nonclassic CAH being the least severe form. Classic CAH is more likely to be diagnosed during infancy and childhood, and nonclassic CAH is likely to be diagnosed as early as childhood or as late as adulthood. NBS=newborn screen.

and/or pubic hair, adult-type body odor, growth acceleration). In adolescence, females can present with irregular menses, acne, and hirsutism. It is much harder to clinically identify males with nonclassic CAH.

DIAGNOSIS

Newborn Screening

Newborn screening for CAH is an effective method for detecting newborns with classic CAH. (15) An early diagnosis of CAH can prevent SW adrenal crises and thereby decrease neonatal mortality. Newborn screening for CAH measures the concentration of 17-OHP, the main steroid precursor that accumulates due to 21-hydroxylase deficiency. 17-OHP levels are measured on a filter paper sample with a blood spot obtained by heel stick of the newborn shortly after birth. (16) Blood samples should be collected 24 hours after birth to avoid false-positive rates due to variation in 17-OHP levels in newborns. As well, preterm infants can exhibit falsely elevated 17-OHP levels. Confirmatory serum 17-OHP can be drawn for diagnostic purposes and to reevaluate borderline samples. (16)

The time at which the specimen is collected for newborn screening is crucial in detecting patients with CAH. The newborn screen should be performed early enough to prevent an adrenal crisis. However, a single newborn screen performed within the first 24 to 48 hours after birth can miss newborns with SV CAH and nonclassic CAH. A second newborn screen on days 7 to 14 after birth can identify more cases of SV CAH and nonclassic CAH due to the later timing of specimen collection. (15)(17)(18) An emerging method of screening for CAH is to measure serum 21-deoxycortisol levels, which are not commonly elevated in newborns and could thereby prevent the high false-positive rates that can be seen in newborn screening for CAH. (19)

Cosyntropin Stimulation Test

The gold standard diagnostic test for adrenal insufficiency is the cosyntropin stimulation test. The cosyntropin stimulation test can confirm cortisol deficiency and excess androgen production in CAH. Cosyntropin is a synthetic derivative of corticotropin which mimics its function in the hypothalamic-pituitary-adrenal axis. (20) In the case of suspected primary adrenal insufficiency, a high dose (250 μg) of cosyntropin is administered to assess endogenous cortisol production, 17-OHP, and androgen levels. Corticotropin-stimulated 17-OHP levels between 1,000 and 1,200 ng/dL typically

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indicate nonclassic CAH, (21) 10,000 ng/dL or greater indicate SV CAH, and 20,000 ng/dL or greater indicate SW CAH. (5) Because classic CAH can involve potentially life-threatening hormone deficiencies, replacement of hormones should be instituted immediately after testing or if testing cannot be performed.

Genetics

CAH is a monogenic disorder with autosomal recessive inheritance. The *CYP21A2* gene is expressed in the adrenal cortex and codes for the 21-hydroxylase enzyme. Pathogenic variants in the *CYP21A2* allele such as deletions, gene conversions, missense, nonsense, and frameshifts can render the gene nonfunctional in CAH. (22) The carrier frequency is 1 in 60 in the general population. (2) A child of 2 carriers has a 25% chance of being affected with CAH, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected.

Genetic testing, although uncommon as a first-line diagnostic tool, can be performed to help diagnose and/or phenotype CAH. Genotyping through full gene sequencing can be complex due to the difficulty in distinguishing carriers from affected patients via the *CYP21A2* locus. Therefore, if gene sequencing is to be performed for diagnosis, the suspected patient and both of their parents should be tested to provide accurate results. To further increase accuracy, specific gene amplification through PCR could be used in addition to full gene sequencing. (5)(23) Although it is more complicated, genotyping of both parents can be useful when considering family planning.

Finally, there is a contiguous gene deletion syndrome called CAH-X syndrome that affects 10% of patients with CAH. (5) These patients exhibit a phenotype similar to Ehlers-Danlos syndrome and characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. (24)(25) CAH-X syndrome involves the deletion of both *CYP21A2* and *TNX-B* genes located in the same region (human histocompatibility complex: 6p21.1-21.3) on chromosome 6 resulting in these patients being *TNX-A/TNX-B* chimeras. (26)(27)

TREATMENT

Medical Treatment in CAH

Medical management of classic CAH aims to provide adequate glucocorticoid replacement and to suppress corticotropin stimulation of the adrenal glands to inhibit excess androgen production. Hydrocortisone is used for cortisol replacement in growing children, typically divided into 3 daily doses, although more frequent dosing might be necessary in some patients to achieve hormonal control. However, patients with classic CAH often require supraphysiological doses at 12 to 15 mg/m^2 per day to achieve adequate androgen suppression. As well, it can be challenging to mimic physiological diurnal cortisol secretion with current immediate-release hydrocortisone and longer-acting glucocorticoid formulations, which, if not mimicked, could then lead to repeated exposures to excess androgen, with subsequent growth acceleration and bone age advancement.

Patients with SW CAH, and certain patients with SV CAH, also require mineralocorticoid replacement with fludrocortisone at a typical dose of 0.1 mg daily. These patients also require sodium chloride supplementation during infancy, given that human milk and infant formulas do not contain adequate sodium, and require additional consumption of salt throughout childhood and adolescence. In addition, females with nonclassic CAH may consider oral contraceptive pills and spironolactone to counteract symptoms of hyperandrogenism such as irregular menses and hirsutism.

Patients with CAH require routine laboratory testing once every 3 months on average to monitor serum 17-OHP, androstenedione, and testosterone levels for glucocorticoid management, as well as plasma renin activity and electrolyte levels for mineralocorticoid and salt management. The endocrinologist can assess and adjust medication regimens based on laboratory values and growth.

Sick-Day Management: Stress Dosing

Patients with CAH have an inadequate cortisol response to stress and require additional stress dosing with hydrocortisone during acute illness (eg, temperature ≥100.4°F [≥38°C], gastroenteritis with dehydration), after physical trauma, or when undergoing procedures requiring sedation. Stress dosing mimics the physiological cortisol stress response and thereby avoids an adrenal crisis. The physiological response to an acute stressor involves a coordinated neuroendocrine mechanism that includes increases in the stress hormones cortisol, epinephrine, and growth hormone. (28) In addition to diminished adrenocortical function, patients with classic CAH exhibit impaired adrenomedullary function as infants, demonstrated by lower epinephrine levels. (28) Epinephrine deficiency in the first year of life is associated with increased risk of illness in CAH infants. (29) Adrenal crisis is associated with increased morbidity and mortality in patients with CAH, (30) especially during the first few years of life, with the most common cause of death being an adrenal crisis after an acute infectious illness. (31) Severe illness in children with CAH can be commonly

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caused by gastroenteritis and accompanied by hypoglycemia, vomiting, and seizures. (32)(33)(34)(35)(36) Signs and symptoms that may indicate an adrenal crisis include electrolyte abnormalities (hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis), low blood pressure, vomiting, diarrhea, and abdominal pain.

Stress dosing should be administered quickly without delay. Moderate illness (eg, fever >100.4°F [>38°C], significant upper respiratory infections) merits an increase in hydrocortisone to approximately 25 to 30 mg/m² per day, divided into 3 to 4 doses depending on the patient's daily dose frequency. Major stress or severe illness (eg, with fever ≥102°F [≥38.9°C], onset of vomiting and/or diarrhea) merits an increase in hydrocortisone to 50 mg/m² per day divided into every-6-hour dosing. Hydrocortisone is the glucocorticoid therapy of choice for oral stress dosing because it is an effective immediate-release medication and is associated with some mineralocorticoid activity. Small frequent sips of fluids containing glucose and salt are recommended for illnesses with vomiting and/or diarrhea.

If a patient cannot keep down the oral medication (eg, repetitive vomiting within 15–20 minutes) or cannot take an oral stress dose (eg, seizure, loss of consciousness), then an intramuscular injection of hydrocortisone should be administered to provide 4 hours of coverage, and the family should be counseled to immediately proceed to the emergency department for evaluation and additional parenteral treatments (intravenous fluids and hydrocortisone). An age-based hydrocortisone dose regimen is as follows: infants and preschool age, 25 mg; school age, 50 mg; older adolescent, 100 mg. (37)

In terms of education, caregivers should receive training from the endocrinology clinic on the administration of an emergency hydrocortisone injection kit (hydrocortisone 100-mg powder for solution for injection or infusion 1 × 2 mL [vial with diluent]) to allow for rapid mixing of hydrocortisone powder and injection diluent. As well, families should have an emergency letter outlining stress dosing and emergency contact information from the child's endocrinologist. Finally, patients should be encouraged to wear or carry with them medical identification stating that the patient has "adrenal insufficiency" and "needs hydrocortisone" in case of an emergency. (38)

Atypical Genitalia

Although the external genitalia in 46,XX females with classic CAH can be partially or even fully virilized (with nonpalpable gonads), the internal reproductive structures (ovaries, fallopian tubes, uterus, and proximal vagina) develop typically and have the potential to function normally later in life with respect to fertility.

Surgical reconstruction of virilized external genitalia in females can be offered to certain patients and include urogenital mobilization, vaginoplasty, labiaplasty, and/or clitoroplasty. There has been debate regarding the extent of procedures to be performed and at which age to perform them. Some may consider clitoroplasty as cosmetic, whereas vaginoplasty can prevent frequent urinary tract infections and allow for improved menstrual flow. Others strongly argue that feminizing genitoplasty surgeries are important for appropriate psychosocial development and avoidance of significant distress related to having virilized external genitalia in these children. (37)

Regardless, clinical practice guidelines state that parents/guardians of virilized females be informed of all surgical considerations. (37) As well, once parents/guardians are made aware of indications, risks, benefits, and the option to forgo surgery altogether, there should then be shared decision making with their physicians. Physicians should be supportive of the decision that the parents/guardian choose and provide appropriate follow-up as needed.

Although prenatal dexamethasone treatment can be administered during pregnancy to prevent virilization of 46,XX females with CAH, the clinical practice guideline advises against it as standard of care due to safety concerns and effects on the fetal brain. (37)

Future Therapeutics

There are novel therapeutics currently under development at the preclinical and clinical trial stages to help provide adequate corticotropin and androgen suppression without causing hypercortisolism in patients with CAH.

A novel delivery of hydrocortisone can help replace cortisol in a more physiological circadian fashion. Modified-release hydrocortisone formulations can mimic endogenous cortisol circadian rhythm, (39) thereby avoiding supraphysiological doses of glucocorticoids and associated morbidity such as short stature, obesity, hypertension, and osteoporosis. (5)(40) This could potentially improve the long-term control of CAH and mitigate effects of supraphysiological doses of corticosteroids. (5)(41)

Another therapeutic innovation geared toward reducing androgen excess in patients with CAH are the corticotropin-releasing factor type 1 receptor (CRF1R) and melanocortin-2 receptor (MC2R) antagonists. CRF1 is a hypothalamic hormone that stimulates the release of corticotropin. Thus,

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using a CRF1R antagonist could potentially inhibit excessive corticotropin signaling that occurs in patients with CAH and reduce androgen excess while allowing for lower replacement doses of hydrocortisone. (42) MC2Rs are found on the adrenal cortex, where corticotropin from the pituitary gland binds to signal androgen production in the adrenal gland. Blocking MC2R could help reduce the effects of corticotropin on the adrenal gland and thereby reduce androgen production. (43)

Last, CAH is a monogenic condition, which makes gene therapy for patients with CAH a possibility for the future. A *CYP21A2* human transgene is in clinical trials to be delivered into patients with the hopes of restoring endogenous adrenal cortical function. Functioning DNA or RNA coding for *CYP21A2* introduced into the body could then potentially alter gene expression and allow for decreased medication doses or the potential to stop taking replacement medications in CAH. (44)

COMORBIDITIES AND LONG-TERM MANAGEMENT/OUTCOMES

Children with classic CAH, in particular, can develop comorbidities over the lifetime that include, cardiovascular disease risk, difference in brain morphology and cognition, and effects on bone health (Fig 4).

Cardiovascular Disease Risk

Children with CAH exhibit almost double the prevalence of obesity compared with their unaffected peers, along with increased abdominal adipose tissue. (45) In general, a centralized fat distribution is more commonly seen in healthy males (android or "apple-shaped" body type) compared with females (gynoid or "pear-shaped"). Android shape is a more unfavorable distribution of fat because abdominal adiposity promotes more inflammation throughout the body. (45) As well, children with CAH exhibit an earlier age at adiposity rebound (the second rise in BMI during childhood) at 1.7 to 3 years compared with 5 to 7 years in unaffected children. (46)

In addition, patients with classic CAH are known to exhibit other cardiometabolic risk factors as early as childhood that include a higher prevalence of hypertension, elevated fasting blood glucose level, and dyslipidemia compared with controls. These risk factors then persist and evolve with age. Children and adults with CAH also exhibit a higher prevalence of nontraditional cardiometabolic

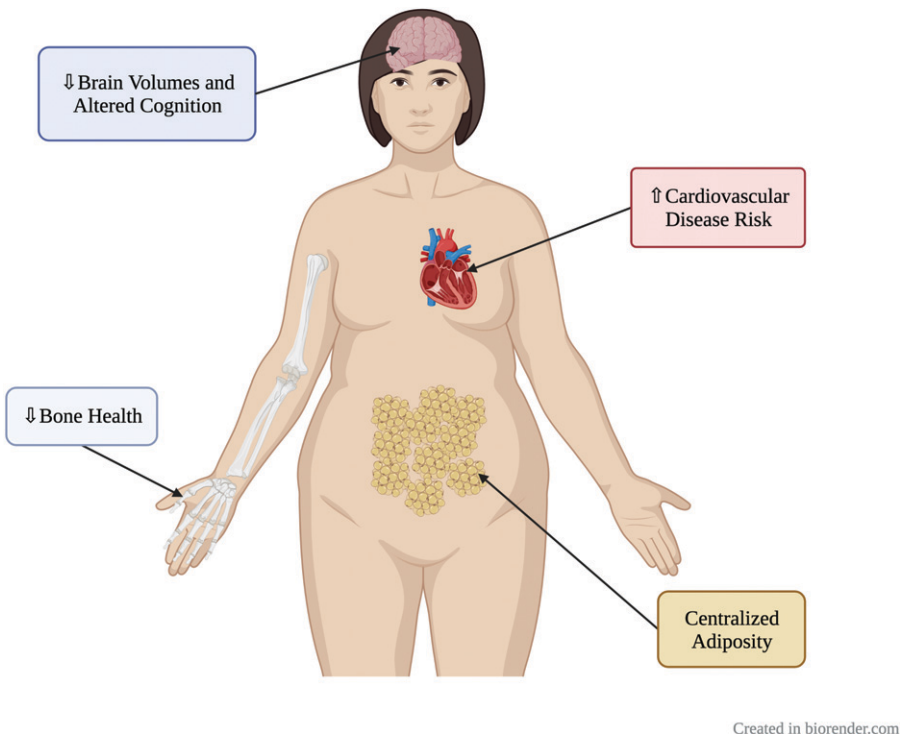

Figure 4. Common comorbidities and potential long-term outcomes in patients with classic congenital adrenal hyperplasia (CAH). Patients with CAH are known to have a higher prevalence of cardiovascular disease risk factors with an increased prevalence of obesity compared with controls. In addition, patients with CAH have decreased bone mineral density and vitamin D deficiency compared with controls. In the brain, individuals with CAH exhibit smaller whole brain volumes, with smaller prefrontal cortex, amygdala, and hippocampal volumes compared with controls, along with cognitive deficits and affected white matter microstructure.

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risk factors such as subclinical atherosclerosis, inflammation, and insulin resistance. (47) Therefore, treatment and early intervention can help minimize comorbid conditions such as obesity and cardiometabolic disease in patients with CAH.

Brain and Cognition

The altered intrauterine environment due to hormone imbalances and postnatal exposures to androgens and glucocorticoid treatment in patients with CAH could influence brain development and function. (5) Children and adults with classic CAH show smaller whole brain volumes, including smaller prefrontal cortex, amygdala, and hippocampal volumes compared with unaffected controls. (48)(49)(50)(51) These key brain structures play important roles in executive functioning and behavioral regulation. Responses by glucocorticoid and androgen receptors throughout the brain could lead to effects from hormone imbalances inherent to CAH and treatments, with both structural and functional changes observed in children and adults with CAH. (48)(49) In addition, changes in white matter microstructure have been observed in patients with CAH compared with controls, specific to the fornix and stria terminalis tracts in the limbic system that are important for memory and emotional regulation. (52)

Furthermore, studies on the cognitive function of patients with CAH have suggested key differences in patients with CAH compared with controls. Overall, children with CAH have shown impaired functioning in visual memory, working memory, and executive functioning. (53)(54)(55) Executive functions include different cognitive functions that are necessary for planning, focusing attention, remembering, and multitasking. Although some studies suggest that these cognitive function deficits are independent of glucocorticoid dosing, other studies suggest that glucocorticoid dose, androgen excess, and number of hyponatremia episodes could be possible causes. (53)(54)

Bone Health

Patients with CAH can also have affected bone health over time, with lower bone mineral density (BMD) observed in adults with CAH compared with controls. (56)(57)(58) Children with CAH have exhibited lower BMD than controls, (59) although other studies have shown normal BMD in children with CAH. (56)(60) High total cumulative and average daily glucocorticoid doses have been associated with decreased BMD in adults with CAH (57)(61); however, dehydroepiandrosterone sulfate and bone age *z* scores have been associated with higher BMD. (59)(62) BMD also was negatively correlated with visceral adipose tissue after adjusting for BMI z score in children with CAH. (59) In addition, adults and children with CAH exhibit vitamin D insufficiency compared with controls. (56)(63) Thus, maintaining regular physical activity and calcium and vitamin D supplementation are recommended for osteoporosis prevention beginning in adolescence. (56)

Adrenal Rest Tumors

Testicular adrenal rest tumors (TART) are benign tumors that arise in the testes in patients with CAH, especially in school-age males with poorly controlled classic CAH. (64)(65) Persistent corticotropin stimulation can lead to the development of ARTs in the testes, which have been observed in 14% to 89% of males with classic CAH. (64)(66) Guidelines currently recommend that males with CAH be screened for TART with scrotal ultrasonography no later than adolescence. (37) There are also recent cases of ovarian ART identified in females with classic CAH, although very rare; there are less than 2 dozen case reports in the literature. OART are often more readily identified on positron emission tomography/computed tomography. (67) Both TART and OART could interfere with reproductive functioning of the gonads, including disruption of menstrual cycles, and in the worst case, secondary infertility. (68)(69)

Summary

- Newborn screening programs that incorporate screening for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency can help identify patients earlier in life and, therefore, mitigate long-term effects. (Based on research evidence) (15)(16)
- When screening for CAH, second-tier screening by liquid chromatography–tandem mass spectrometry can help improve the positive predictive value of CAH screening. (Based on research evidence) (15)(17)(18)
- Pregnant women with a fetus who may be affected by CAH should only consider prenatal dexamethasone therapy only from a center with a protocol approved by the institutional review board so that the risks and benefits of this nonstandard treatment are clear. (Based on research evidence as well as consensus) (37)

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- Infants with a positive newborn screen for CAH should be referred to pediatric endocrinologists. (Based on common clinical practices) (37)
- When diagnosing CAH past infancy, it is important to obtain laboratory values for 17-hydroxyprogesterone in the early morning (8 AM) to get the most accurate results. (Based on research evidence) (15)(17)(18)
- For pediatric patients with CAH, treatment with hydrocortisone is recommended. (Based on research evidence) (5)(22)
- For infants with CAH, fludrocortisone and sodium chloride supplements are recommended in addition to hydrocortisone treatment. (37)
- It is important to monitor patients with CAH for signs of mineralocorticoid deficiency and excess. (Based on research evidence as well as consensus) (37)
- For patients with CAH who are receiving glucocorticoid treatment who are in increased stress situations such as febrile illness, major surgery using anesthesia, major trauma, or gastroenteritis with dehydration, it is important to increase the glucocorticoid dose. (Based on research evidence) (37)
- Patients with CAH should always wear or carry medical identification indicating that they have adrenal insufficiency. (Based on research evidence as well as consensus) (38)
- Parents, guardians, and close contacts of a child with CAH should be educated on adrenal crisis prevention, increasing glucocorticoid dosing during illness, and administration of emergency glucocorticoids. (Based on consensus) (37)
- Patients with CAH and their families should be equipped with a glucocorticoid injection kit for emergencies. (Based on research evidence as well as consensus) (37)
- For asymptomatic, nonpregnant patients with nonclassic CAH, glucocorticoid treatment is recommended. (Based on research evidence) (5)(37)

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PIR QUIZ

1. A 5-day-old infant is brought to the emergency department due to lethargy and poor feeding. The newborn screening results are pending. On physical examination, the baby has hyperpigmented nipples and external genitalia, along with bilateral cryptorchidism. The patient is exclusively breastfed without any supplementation and has started vomiting after feedings. Confirmatory laboratory studies for congenital adrenal hyperplasia (CAH) are drawn, including 17-hydroxyprogesterone (17-OHP), androstenedione, testosterone, and plasma renin activity. The chemistry panel reveals hyponatremia and hyperkalemia. The patient is started on intravenous saline and corticosteroids. Which of the following additional testing should be considered for this patient?

   A. 24-hour serum cortisol level.
   B. Karyotype.
   C. Magnetic resonance imaging of the brain.
   D. Spot urine sodium level.
   E. Renal ultrasonography.

2. The newborn screen of a male infant drawn 36 hours after birth is reported as positive for CAH. Which of the following is the most appropriate, immediate next step?

   A. Check morning serum cortisol level.
   B. Initiate dexamethasone therapy.
   C. Initiate hydrocortisone and fludrocortisone therapy.
   D. Perform abdominal ultrasonography.
   E. Obtain serum 17-OHP level.

3. A 7-year-old girl is brought to the pediatric clinic to establish care as a new patient. She was born at term, without complications. Newborn screening performed in the first week of life was normal. Her family does not report any significant medical history, including surgeries and hospitalizations. You note that she is at the 90th percentile for height despite having a midparental target height of 162 cm. Physical examination is notable for hyperpigmented gums, acne, axillary hair, and Tanner 3 pubic hair. On further questioning, the parents recall that she developed adult-type body odor and acne 2 years earlier. A subsequent steroid panel shows elevated 17-OHP, androstenedione, and testosterone levels. Which of the following would confirm an intrinsic adrenal gland defect?

   A. Cosyntropin stimulation test.
   B. Karyotype.
   C. Magnetic resonance imaging of the brain.
   D. Random serum cortisol level.
   E. Renal ultrasonography.

4. A newborn is diagnosed as having CAH and is started on therapy. In discussing the long-term complications of CAH despite therapy with the parents, which of the following is a potential long-term complication of CAH?

   A. Cardiomyopathy.
   B. Cirrhosis.
   C. Coagulopathy.
   D. Decreased bone mineral density.
   E. Increased intracranial pressure.

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5. A 16-year-old girl presents to your afternoon clinic with irregular menses since menarche at 14 years of age. She is mildly obese with cystic acne along her jawline and dark chin hairs. She is not sexually active. To evaluate for nonclassic CAH as part of your differential diagnoses, which of the following diagnostic testing should be considered?

   A. Bone age.
   B. Midcycle serum progesterone level.
   C. Midcycle serum testosterone level.
   D. Morning serum 17-OHP level.
   E. Postclinic serum 17-OHP level.

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