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Congenital Adrenal Hyperplasia: A Clinical Review

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Abstract

CYP21A2 genes code for 21-hydroxylase (21OH), an enzyme required for the production of cortisol and aldosterone by the adrenal cortex. Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that occurs when both copies of a patient's CYP21A2 genes are mutated and their ability to produce the adrenal cortical hormones cortisol, and also aldosterone in severe cases, is compromised but their production of adrenal androgens is increased. Neonates with severe CAH will experience life-threatening acute adrenal crisis unless promptly diagnosed and appropriately managed. CAH-induced adrenal crisis presents most critically with hypotension, hyponatremia, hypoglycemia, and hyperkalemia, as well as with less specific symptoms (fatigue, nausea, and vomiting). CAH is also the most common cause of androgenized genitalia in 46XX newborns. Patients with severe CAH will require lifelong hormone replacement and "sick day" dosing in response to physiologic stressors. Adults with CAH face lifelong health challenges, many associated with reproduction. Thus, a practitioner including an advanced practice nurse could encounter a patient with CAH in the emergency department or primary care office. This clinical review discusses the pathophysiology, presentation, diagnosis, and management of CAH. Its goal is to prepare advanced practice nurses and other practitioners to recognize CAH and contribute to the care of patients with CAH across the lifespan, with the goal of reducing complications.

Keywords: *Congenital Adrenal Hyperplasia, Cah, Virilized Genitalia, Adrenal Crisis.*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder in which a patient's ability to synthesize cortisol (and sometimes also aldosterone) is reduced or absent. Some 90-95% of patients with CAH have two mutated CYP21A2 genes, which code for 21-hydroxylase (21OH), an enzyme required for the production of cortisol and aldosterone by the adrenal cortex.[1,2,3] Although there are other rare causes of CAH,[4] 21OH deficiency (21OHD) caused by CYP21A2 mutations is the most likely form a practitioner will encounter and the focus of this review.

CAH is the most common cause of androgenized genitalia in 46XX newborns and potentially life-threatening adrenal insufficiency in young children.[3,5] Patients with severe CAH will require lifelong glucocorticoid and mineralocorticoid therapy, as well as careful management during times of stress.[6,7] However, those with milder forms of CAH may not develop issues of concern until later in childhood or even as adults.[8,9,10] Thus, practitioners may encounter patients with CAH in settings from primary care to acute care.

This clinical review provides an overview of the pathophysiology, presentation, diagnosis, and management of CAH across the lifespan. It applies basic science concepts to explain the diagnostic testing strategies, pharmacologic interventions, and patient education approaches advanced practice nurses will need to contribute to the early diagnosis and proper management of CAH with the goal of reducing CAH-related complications. Treatment recommendations for chronic and emergency care of patients with CAH are outlined in tables 1 through 4. Treatment goals at each stage of life for patients with CAH are included in the text. The final section of the paper discusses possible approaches for the advanced practice nurse to engage with patients living with CAH. A summary of the health challenges faced by patients with CAH is included in table 5.

GENETICS AND INHERITANCE

CYP21A2, the gene responsible for CAH when mutated, is located on chromosome 6 near the tenascin X active gene (TNXB). (See Figure 1.) TNXB codes for a component of normal collagen.[1,5] Over 300 deleterious mutations of CPY21A2 have been identified; the vast majority (>90%) of these mutations are deletions.[2,11] Deletions in CYP21A2 may inactivate TNXB as well. Consequently, about 10% of patients with CAH have CAH-X syndrome in which a person inherits both CAH and the hypermobile joints characteristic of Ehlers–Danlos syndrome.[5]

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CAH is divided into a more severe but less common "classic" and a less severe but more common "non-classic" type (NCCAH). Classic CAH is further categorized into salt wasting (SWCAH) or simple virilizing (SVCAH) subtypes. (In this article, the term "androgenized" is used rather than "virilized" to provide more accurate and neutral language.) The severity of CAH is determined by the level of residual 21OH activity (Table 1).[1,12] The most severe type of CAH is SWCAH, which occurs when the level of 21OH activity is so low that both aldosterone and cortisol production are inadequate.[13] Table 1 also demonstrates that non-classic CAH is at least an order of magnitude more common than the more severe classic type.

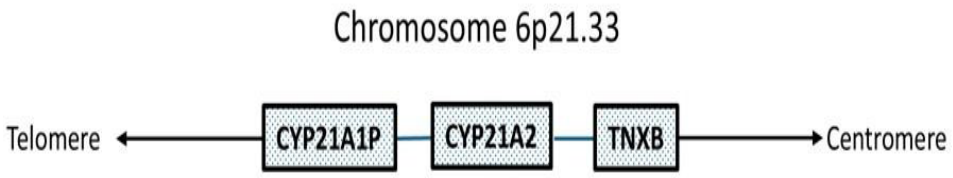

Figure 1. shows the 21st region of the short (p) arm of chromosome 6 (6p21,33) where CYP21A2 (the gene responsible for CAH when mutated) is located. This region also contains a very similar but inactive pseudogene (CPY21A1P) and the tenascin X active gene (TNXB). Most mutations of CYP21A2 are generated by misalignment and improper crossing over between CPY21A2 and CPY21A1P during meiosis I with deletion of part of CPY21A2 The proximity of CYP21A2 to TNXB explains why loss of material from CYP21A2 can be accompanied by inactivation of TNXB as well.[1,5]

Table 1. CAH Subtypes

	Classic		**Non-Classic (NCCAH)**
	Salt wasting (SW)	**Simple virilizing (SV)**	
Incidence/ live births	1: 10,000-20,000		1: 200-2,000
% normal 21OH activity	< 1%	1 – 2%	20 – 50%
Age of presentation	Infant	Infant	Childhood / Adulthood
GC required	+	+	+/-
MC required	+	+/-	-
↑ androgen production	+	+	+
46XX virilization	At birth	At birth	Childhood

Subtypes of CAH with clinical characteristics of each.[1,2,3,6,7,12] GC indicates glucocorticoids; MC indicates mineralocorticoids. (+/-) indicates that this treatment is required for some but not all patients and most often required during infancy/ childhood.

Because CAH is an autosomal recessive disorder, patients with CAH must have two mutated CPY21A2 genes. However, most people with CAH are compound heterozygotes; they have different mutations on each gene.[10] There is good genotype to phenotype correlation (at least for some mutations) and the level of residual 21OH activity (and thus the severity of CAH) is determined by the less severe mutation.[14] However, the majority of people with the less severe form (NCCAH) carry one CPY21A2 allele that would produce severe classic CAH if it were present in two copies.[10] Consequently, a couple in which both partners have the less severe form (NCCAH) could have a child with either NCCAH or more severe classic CAH. While the classification system for CAH described above guides treatment decisions,[6,7] CAH phenotypes are most accurately considered as a continuum[1,12] and all patients with classic CAH have some degree of increased sodium excretion.[5]

PATHOGENESIS

The adrenal cortex consists of 3 layers: the zonas glomerulosa, fasciculata, and reticularis. Normally, cholesterol is converted to mineralocorticoids (aldosterone) in the glomerulosa upon stimulation by angiotensin II. Cholesterol is converted to glucocorticoids (cortisol) in the fasciculata, and to androgens in the reticularis upon stimulation by adrenocorticotropin (ACTH) from the anterior pituitary gland.[11] (See Figure 2.) ACTH (and thus cortisol) levels vary with diurnal rhythms and increase in response to stress.

The adrenal cortex converts cholesterol to cortisol and aldosterone via multiple intermediates. Both of these processes require the enzyme 21OH. Thus, patients with CAH may be deficient in both cortisol and aldosterone. They may also have elevated androgen levels both because precursors to the enzymatic step normally driven by 21OH accumulate and these precursors can be converted to androgens[3,16] (see Figure 3) and because a lack of cortisol will elevate ACTH release from the anterior pituitary gland.[1] (See Figure 2.)

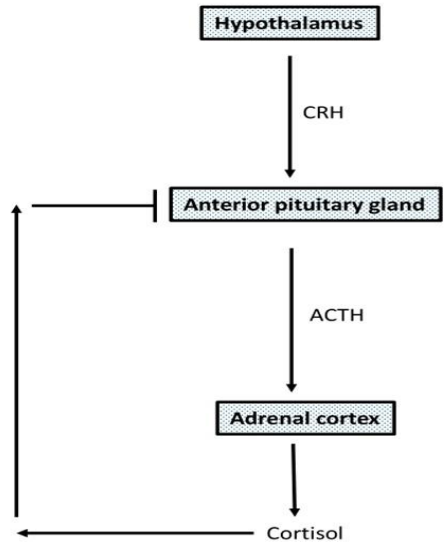

Figure 2 shows the hypothalamic, anterior pituitary gland, adrenal cortex axis. Note that the hypothalamus exerts a stimulatory effect on adrenocorticotropic hormone (ACTH) release from the anterior gland via corticotropin releasing hormone (CRH). ACTH from the anterior pituitary gland then exerts a stimulatory effect on the adrenal cortex leading to cortisol release. However, the cortisol exerts a negative feedback effect on the anterior pituitary gland.[1,2,3,5]

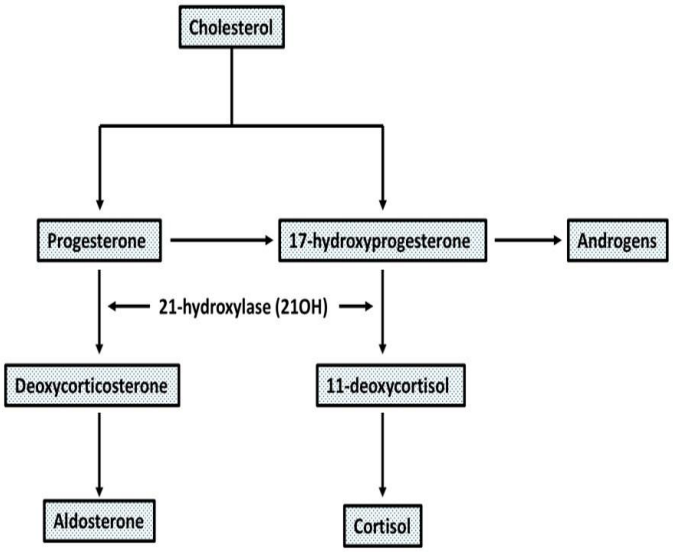

Figure 3 shows the metabolic pathways by which steroid hormones are produced from cholesterol in the adrenal cortex. The adrenal gland converts cholesterol to 17-hydroxyprogesterone and progesterone via multiple intermediates. The enzyme 21-hydroxylase (21OH) then converts 17-hydroxyprogesterone to the cortisol precursor 11-deoxycortisol and progesterone to the aldosterone precursor deoxycorticosterone. However, 17-hydroxyprogesterone and progesterone can both be converted to androgens as well.[3,16] Thus, patients with CAH (and thus inadequate 21OH function) may be deficient in aldosterone and cortisol. They may also have elevated androgen levels, both because androgen precursors accumulate in their adrenal cortex cells and because their androgen production is stimulated by high ACTH levels from lack of negative feedback by cortisol to the anterior pituitary gland.[1,5]

High androgen levels during fetal development are responsible for the androgenized genitalia seen in 46XX newborns with CAH.[5,14,16] (Excellent line drawings showing the process of fetal genital development and the varying levels of genital androgenization in 46XX newborns with classic CAH are available in several sources.[1,2,3]) Patients with classic CAH are also at risk for acute adrenal insufficiency (Addisonian crisis) because they are not able to increase cortisol and aldosterone production in response to physiologic stress.[8] Treatment for CAH seeks to replace missing hormones and to normalize androgen levels with a goal of reducing CAH-related complications.[2]

CLINICAL PRESENTATION, DIAGNOSIS, AND MANAGEMENT

People with CAH have health challenges and increased mortality risk throughout life with each individual's health challenges determined by their disease severity and age.[2,17,18,19]

Prenatal Diagnosis and Prevention of Androgenization

Because androgenized genitalia can cause emotional distress and functional problems for females with CAH, couples in which both members carry a single mutated CYP21A2 gene (often a couple that has already given birth to a child with CAH) may seek fetal genetic testing during subsequent pregnancies.[1,20] Dexamethasone is a glucocorticoid that crosses the placental barrier intact. It can be administered to the pregnant woman to suppress ACTH (and thus androgen) production in a fetus with CAH and will limit genital androgenization if the fetus is 46XX. However, because androgenization begins early in fetal development, this treatment must be started by gestational week 7 to be effective.[2]

Cell-free fetal DNA testing of maternal blood for the SRY (sex-determining region of Y chromosome) can be performed as early as 6 weeks gestation and will separate 46XY fetuses (who will not benefit from dexamethasone) from 46XX fetuses who might. However, if dexamethasone is administered based on this maternal blood test alone, unaffected 46XX fetuses will still be exposed to dexamethasone, at least until full fetal genetic testing can be performed at 10-12 weeks gestation to determine if the fetus actually has CAH.[2] It is important to limit the number of fetuses that are exposed to dexamethasone because maternal treatment with glucocorticoids may increase the risk of birth defects (e.g. cleft lip/ cleft palate) and lower birth weight as well as producing longer-term impacts on behavior and cognition as the child grows.[1] Thus, prenatal treatment for CAH is not currently recommended.[6]

Neonates and Infants

Most neonates with clinically significant CAH are identified by elevated 17-hydroxyprogesterone levels on newborn bloodspot screening.[3] (17-hydroxyprogesterone is a cortisol

precursor that accumulates in patients with 21OH deficiency. See figure 3.) Those with classic CAH generally have values far above the normal cutoff, although neonates with NCCAH may have equivocal results and a secondary screening using a challenge with the synthetic ACTH analogue such as cosyntropin (increases 17-hydroxyprogesterone in patients with CAH, see figure 2) is recommended by current guidelines from the US and Japan.[6,7] Genotyping to diagnose CAH is also an option. However, given the large number (>300) different mutations of the CYP21A2 gene that can cause CAH and the incomplete understanding of genotype-phenotype correlations[2], interpretation of genotype results is complex, and genotyping is considered a third-tier diagnostic approach. It is recommended only when 17-hydroxyprogesterone screening and a cosyntropin challenge have not produced clear results.[6]

Newborn bloodspot screening can produce false negative results if the mother received prenatal glucocorticoids and false positive results in sick or premature neonates (and even healthy babies within 2 days of birth) however.[11] Practitioners should consider the gestational age / size and health status of the neonate, and the timing of the test, in interpreting CAH screening results.[1,7] Current guidelines from both the US and Japan strongly support universal screening of neonates for CAH and recommend that newborns who test positive be referred to a pediatric endocrinologist.[6,7]

46XX neonates with classic CAH (SW or SVCAH) will have androgenized genitalia induced by the elevated levels of androgens to which they were exposed *in utero*.[5,16] The degree of androgenization is described by the Prader scale from stage 1 (normal vagina with slight enlargement of clitoris) to stage 3 (greatly enlarged clitoris, a single urogenital meatus, and nearly fused labia) to stage 5 (fully fused labia and a urethral meatus at what appears to be the glans penis).[2,20] Neonates with NCCAH generally do not display androgenized genitalia at birth[2,14] and neither do genetically normal 46XX babies born to women with CAH because the placenta expresses the aromatase enzyme which converts maternal androgens to estrogens.[1] The genitalia of otherwise normal 46XY newborns are not noticeably affected by CAH.[3,21]

Given the possibility of false negative newborn screening results and the risk of fatal adrenal crisis in undiagnosed newborns with classic CAH, it is important that advanced practice nurses entertain the possibility of classic CAH in apparently male neonates with bilateral cryptorchidism.[3] Karyotyping to distinguish 46XX from 46XY neonates may be helpful in this instance. Neonates with SWCAH will become critically ill (develop an adrenal crisis) if not promptly diagnosed and properly managed, generally by a specialist. However, these neonates often do not experience an adrenal crisis until > 5 days after birth, when they are likely to be at home,[12] making proper diagnosis prior to discharge vital.

The normal response to the stress of infection involves the release of cytokines which stimulate the hypothalamus and increase cortisol production. However, infection can precipitate an adrenal crisis in neonates with classic CAH whose adrenal glands cannot respond appropriately.[8] About ¾ of neonates with untreated classic CAH experience an adrenal crisis by 3 weeks of age.[5]

Practitioners may encounter neonates and infants with CAH-induced adrenal crisis in acute care settings where they present most critically with hypotension, hyponatremia, hypoglycemia, and hyperkalemia, as well as with less specific symptoms (fatigue, nausea, and vomiting).[5,8] The electrolyte imbalances result from lack of aldosterone (increases sodium reabsorption and potassium secretion by the nephron)[16] while the hypoglycemia results from lack of cortisol (stimulates gluconeogenesis).[13] The hypotension of an adrenal crisis is multifactorial with hypovolemia secondary to inadequate renal sodium reabsorption, poor vasoconstriction in response to endogenous catecholamines (cortisol is permissive to the normal action of epinephrine), and poor maturation of the adrenal medulla (requires cortisol) all playing a role.[5,16] Recommended treatments for children and adults with CAH experiencing an acute adrenal crisis are given in Table 2. Given the complexities of CAH diagnosis described above[2,6] and the potentially fatal consequences of acute adrenal crisis[5,8] a neonate with suspected CAH (e.g. a 46XX newborn with androgenized genitalia) who has not received a firm diagnosis of CAH may benefit from empiric treatment with cortisol.

Table 2. Recommended treatments for acute adrenal (Addisonian) crisis in CAH

Treatment	Children	Adults
IV fluids: 0.9% saline		
Initial dose	20 ml/kg in 1st hour	1000 ml in 1st hour
Repeat doses	Up to 60 ml/kg as required	Individualized for patient
Hydrocortisone (IV)		
Initial dose	50-100 mg/m^2	100 mg
Repeat doses	50-100 mg/m^2/day	100-200 mg/day
Dextrose (for hypoglycemia)	As needed	As needed

Recommended treatments for children and adults with CAH experiencing acute adrenal crisis.[1,20] Note that hydrocortisone doses far in excess of maintenance (Table 3) and fluid resuscitation with isotonic saline are the mainstays of this treatment.

Childhood

If they are producing adequate aldosterone to maintain fluid and electrolyte balances, children with previously undiagnosed CAH (usually NCCAH) are often encountered in primary care by four years of age with the consequences of androgen excess (growth of pubic hair, rapid increases in height, and enlargement of the clitoris in girls). Diagnostic testing for these children includes the ACTH analogue (cosyntropin) stimulation test and the goal of treatment is to control their symptoms with glucocorticoids.[2,5,14] It should be noted, however, that children (and indeed adults) with classic CAH will probably require lifelong maintenance with both glucocorticoids and mineralocorticoids (Table 3).

Table 3. Recommended maintenance medications for classic CAH

Treatment (daily dose)	Children	Adults
Hydrocortisone	10-15 mg/m2	15-25 mg
Fludrocortisone	0.05-0.2 mg	0.05-0.2 mg
NaCl	1-2 g 17-24 mEq/day for infants	

Recommended maintenance treatments for children and adults classic CAH.[1,6,7] Other glucocorticoids may be substituted for hydrocortisone for adults. However, in pediatric patients, hydrocortisone is recommended over longer acting glucocorticoids because it reduces the risk of drug side effects.

Androgens stimulate linear growth but also cause early closure of the epiphyseal plates of long bones.[11] Consequently, young children with CAH and androgen excess grow more quickly than their peers and are taller as pre-teens but reach full height at a younger age. They are shorter by teenage and have reduced adult height.[16,22] This is one of the complications of CAH that practitioners seek to avoid with adequate glucocorticoid suppression of ACTH. Practitioners should also be careful to avoid overtreatment of children with CAH with glucocorticoids as this may also negatively affect adult height.[21]

Another issue, impacting as many as 2/3 of children with classic CAH, is hypertension.[22] High androgen levels may contribute to this hypertension, but excessive treatment with glucocorticoids and mineralocorticoids can also play a role. Pediatric patients with CAH who do develop hypertension are at greater risk for cardiovascular complications as adults.[9] Thus, practitoners should avoid both under and overtreatment of CAH patients with gluco-/mineralocorticoids.

Guidelines from both the US and Japan propose that practitioners should carefully monitor children with classic CAH for glucocorticoid excess and treat patients with NCCAH based on symptoms rather than endogenous hormone levels.[6,7,14] This monitoring includes blood pressure (hypertension may indicate excessive glucocorticoid or mineralocorticoid treatment), linear growth rate and bone age (fast linear growth and early bone maturation may indicate undertreatment with hydrocortisone while slow growth and maturation may indicate overtreatment), and measurement of 17-hydroxyprogesterone and androgen levels[6] (excess levels indicate inadequate hydrocortisone treatment, see figures 2 and 3).

Children with NCCAH who are asymptomatic usually do not require treatment. An exception to this is adolescents with early onset of puberty and bone age that exceeds their chronological age. These patients may be treated with hydrocortisone, at least until they reach full growth potential, with careful consideration of the side effects of such treatments. By contrast, it is usually best to treat adult females with NCCAH who develop hirsutism with oral contraceptives (assuming they do no wish to become pregnant) and androgen blocking medications.[6,14]

Because children with CAH who are receiving glucocorticoid treatment will not be able to increase their cortisol production in response to stress, they will need supplemental hydrocortisone when ill or otherwise subjected to physical stressors to avoid acute adrenal crisis. Febrile illness, trauma, and surgery will all require these “sick day” doses.[1,6] Some sources report that, for patients with CAH, respiratory illness is the most common trigger of adrenal crisis in children while gastroenteritis is the major cause in adults.[8]

Practitioners should educate caregivers to recognize the need for sick day hydrocortisone dosing in their child with CAH who receive hydrocortisone and to promptly administer the medication at home, including by intramuscular injection if the child is vomiting.[3] Preparation for sick day hydrocortisone dosing should include keeping an emergency kit and patients with CAH should avoid fasting during acute illnesses. All patients past early childhood who require treatment for CAH also should wear an emergency bracelet indicating that they have adrenal insufficiency.[6] Recommended sick day doses of hydrocortisone are given in Table 4.

Table 4. Recommended hydrocortisone dose for stressed patients with CAH (For patients receiving maintenance hydrocortisone)

Scenario	Children	Adults
Home		
Major illness	3x normal divided into 4 doses	Add 20 mg TID to usual dose
Fever > 39° C	3x normal divided into 4 doses	Add 20 mg TID to usual dose
Gastroenteritis	3x normal divided into 4 doses	Add 10-20 mg TID or QID to usual dose
Minor illness or fever < 39° C	2-3x normal divided into 3-4 doses	Add 10 mg TID to usual dose
In clinic		
Major surgery	50 mg/m^2 IV bolus then continuous infusion	50-100 mg IV bolus then continuous infusion
Short procedure	50 mg/m^2 IV bolus	50-100 mg IV bolus

Recommended "sick day" hydrocortisone doses by patient age and type of stressor.[1,6]

Surgical correction of androgenized genitalia in 46XX children with CAH is possible[3] but the procedures are technically complex and should be performed by specialists at referral centers. While early surgical correction of androgenized genitalia in 46XX infants with CAH is no longer the standard of care,[1] it may still be considered if androgenization is severe (e.g. urogenital sinus).[6,12] However, results from cosmetic feminizing surgery performed on patients with ambiguous genitalia (the majority of whom had CAH) were judged as "good" in only 18% of cases in one study and further surgeries may also be needed.[23] Current guidelines from both the US and Japan on surgery advise joint decision-making that includes informed input from parents (and patients if sufficiently mature).[1,6,7] Practitioners may also inform concerned parents that adequate glucocorticoid therapy during childhood can reduce the length of the clitoris of a 46XX infant with CAH by ½ from that observed at birth. This also argues in favor of delaying surgery if the concerns are primarily cosmetic.[2]

Hormonal changes during puberty make care of patients with CAH particularly challenging during their transition to adulthood. Higher hydrocortisone doses may be needed during this period[1] but patients who were receiving mineralocorticoids as children may need reduced doses of these medications to avoid hypertension as they enter adulthood.[9] As children with CAH age, they will encounter additional health issues including quality of life challenges, particularly in "school functioning".[24] Careful gluco-and mineralocorticoid doses assessment and psychosocial support is recommended during this period.[1]

Adulthood

Health challenges for patients with CAH continue into adulthood[2,5] and the goal of treatment for adults with CAH is a continuation of the goals in childhood – ensuring proper levels of gluco- and mineralocorticoids while suppressing overproduction of androgens.[1] All-cause mortality for adults with CAH is 2.8 to 5.9 times that of controls, depending on the population studied, with the most frequent causes of death being adrenal crisis, cardiovascular disease, cancer, and suicide. Those with CAH were also 30-40% more likely to experience depression than controls and 16% were judged "non-compliant" with medication prescriptions.[17,18]

Many of the ongoing health challenges for adults with CAH revolve around reduced fertility and reproductive tumors. Women with classic CAH (particularly SWCAH) are less likely to pursue pregnancy and have fewer children than controls.[10] The reasons for this reduced fertility are multifactorial. Women with CAH who have had genital reconstruction surgery may experience impaired clitoral sensitivity and dyspareunia[25] and those with androgenized genitalia may have psychosocial barriers to intimacy.[5]

Women with CAH may also have reduced fertility secondary to menstrual irregularities resulting from excesses in the androgen/aldosterone precursor progesterone and androgens themselves (converted to estrogen by aromatase). These hormonal imbalances disrupt pulsatile secretion of gonadotropins (FSH and LH) from the anterior pituitary gland, thin the uterine lining, and thicken cervical mucus, all of which are barriers to conception. Menstrual regularity is improved by adequate glucocorticoids dosing in some but not all cases.[10,12,19] For women who are experiencing difficulty conceiving, inadequately suppressed progesterone levels during the follicular phase of the ovarian cycle may be the cause.[6] Women with CAH are also at increased risk for polycystic ovarian syndrome[9] which can both contribute to and be caused by anovulatory states. Despite these challenges, 60-80% of women with classic CAH are fertile but they often require cesarean section.[6]

Men with classic CAH also face health challenges that can reduce their sperm count by ½ or more and compromise their fertility. High levels of adrenal androgens suppress gonadotropin release thus compromising spermatogenesis.[5,11,19] Additionally, 50% to 90% of men with classic CAH develop testicular adrenal rest tumors (TARTs). TARTs are generally bilateral, painless until they reach palpable size, and almost always benign. However, because they commonly occur at the mediastinum of the testes (area where the rete testis collects spermatozoa from the seminiferous tubules) they compromise spermatozoa transport and fertility.[3,11,19]

While the embryologic origin of these tumors is unclear, TARTs are ACTH sensitive. Good control of CAH-induced androgens with appropriate glucocorticoids suppresses ACTH production and may reduce (but not eliminate) TART risk and even shrink existing TARTs.[5,19,26] Current guidelines suggest that males with CAH be followed for TARTs with testicular ultrasound beginning at puberty and continuing every 1 to 2 years, and that patients with CAH who are experiencing reduced fertility be referred for specialist care.[6] It has also been suggested that practitioners use the term "tissue" rather than "tumor" when discussing TARTs with patients to avoid patients developing the mistaken belief that these tumors are malignant.[2] However, practitioners should be aware that patients with CAH may also be at increased risk for malignant adrenal myelolipomas.[27]

Adults with CAH are also at increased risk for a range of complications resulting from high androgen levels and/or over-treatment with gluco/ mineralocorticoids.[19] CAH, and its treatments, increase patients' risk for obesity, hypertension, dyslipidemia, and elevated plasma glucose levels.[3,14,19,28] These risk factors predispose a person with CAH to cardiovascular disease and must be carefully managed. Practitioners should consider reducing mineralocorticoid doses in patients with SWCAH and hypertension.[13]

Glucocorticoids also stimulate the activity of osteoclasts while inhibiting osteoblasts,[15] putting patients receiving these medications at risk for osteoporosis. While the evidence is incomplete, higher glucocorticoid doses appear related to greater decreases in bone mineral density (BMD) and higher fracture risk for patients with CAH.[19] Current guidelines suggest baseline BMD measurement in adolescence for patients with CAH who are receiving glucocorticoids with repeat screening in adulthood for those receiving above average glucocorticoid doses.[6]

EMERGING TREATMENTS

Proper dosing of hydrocortisone for patients with CAH is challenging. Children with classic CAH require daily hydrocortisone maintenance with doses based on body size (Table 3) but tablets may not be available in sufficiently low doses for smaller children. One approach to this issue is the development of capsules containing encapsulated microtablets ("sprinkles") that can be administered in divided doses. However, these preparations are much more expensive than standard hydrocortisone tablets.[21]

Given its short serum half-life (~90 minutes), it is also challenging to prescribe a hydrocortisone regimen that maintains the continuous drug levels needed to suppress ACTH release and mimics the normal diurnal rhythm of cortisol levels (lowest levels at night, highest in the morning). QID dosing may be helpful, however this regimen is not always practical. Sustained release hydrocortisone preparations, already approved in Europe for the treatment of adrenal insufficiency from other causes, are being studied for CAH.[29] Additional approaches to improved CAH treatment target reducing androgen production by either blocking CRH receptors in the anterior pituitary gland or inhibiting an enzyme (CYP17A1) needed for the production of androgens by the adrenal cortex.[5,21]

ENGAGING WITH THE PATIENT WITH CAH

CAH is a life-long chronic condition that can produce periodic life-threatening complications. As is the case for chronic illnesses in general, the patient (or caregiver when the patient is very young) should take the lead in managing their disease with the practitioner acting as coach, advisor, and educator.[30] The clearest example of this is the requirement that caregivers be able to assess the need for "sick day" cortisol doses in children with CCAH and administer the required medications both quickly and correctly to prevent adrenal crisis.[3] Centering the patient in all health-related interactions and providing the patient with the information and education they need to set their own treatment goals will help reduce noncompliance with complex treatment regimens, as exist for CAH.[31] This patient centered approach is important even for children and adolescents because it allows them to build the self-management skills they will need as adults.[32]

Some 46XX patients with classic CAH may identify as having differences in sexual development (DSD). (DSD is a term that is replacing "intersex" to identify people whose sexual phenotype cannot be easily described as male or female.[33]) Depending on how DSD is defined, this is a small minority of patients with CAH because classic CAH, with produces androgenized genitalia at birth in 46XX individuals, is an order of magnitude less common than NCCAH, which does not.[3] However, this is a population with specific needs. When treating patients with DSD, practitioners should avoid referring to androgenized genitalia in stigmatizing terms (e.g. use "differences" rather than "disorders of sexual development").[33] The most important attributes of their interactions with practitioners that people with DSD identify are the need for optimum communication with practitioners, the ability of practitioners to act as educators for the patient and their family, and the willingness of practitioners to center patient values in treatment.[34]

The 46XX newborn who presents with androgenized genitalia (high Prader scale score) may be classified as having a DSD. However, in this setting, DSD is an "umbrella term" that has little specific meaning and serves only as the beginning of the evaluation and diagnostic process.[35] None the less, there are general management rules that should be followed. Care, including gender assignment, should be conducted by a specialist at the head of a multidisciplinary team in an appropriate care center. Importantly, given the distress that a newborn with DSD will produce and the social stigma around DSDs, the family's concerns should be addressed in an open, respectful manner, and the family should be included in all decision making.[36]

CONCLUSION

CAH is an autosomal recessive disorder that causes inadequate 21OH activity and compromises cortisol and aldosterone production by the adrenal cortex. Depending on the severity of their disease, patients with CAH may be at risk for life-threatening adrenal crisis and a range of chronic health challenges depending on their age. (A summary of the health challenges faced by patients with CAH is provided in Table 5.) Patients with CAH may require life-long treatment with gluco- and mineralocorticoids with the goal of reducing CAH complications without producing unwanted side effects of overtreatment. They will also require careful management during stress. 46XX newborns with the more severe classic CAH will have some degree of androgenized genitalia and should be treated by an experienced team headed by a specialist. Throughout live, people with classic CAH will benefit from ongoing care from an endocrinologist.

Table 5. Summary of health challenges for patients living with CAH

Response / system	CAH patient population	Challenge
Stress response	Most severe in classic CAH	Reduced response Addisonian crisis from stress/ injury
Genitalia	46 XX newborns with classic CAH	Varying degrees of androgenization
	46 XX children with NCCAH	Enlarging clitoris in childhood
Linear growth	Patients with elevated androgens	Rapid growth as preteens Reduced adult height
Blood pressure	Patients with elevated androgens or those overtreated with steroids	Hypertension from childhood. Consequences of hypertension as adults
Other responses to steroids	Patients treated with steroids	Obesity, dyslipidemia, elevated plasma glucose, osteoporosis
Reproductive system	Women	Reduced fertility Polycystic ovarian disease
	Men	Reduced fertility TARTs Adrenal myelolipomas

Summary of health challenges faced by patients with CAH.

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