Congenital Adrenal Hyperplasia in the Adolescent

Mimi S. Kim, Teresa Tseng, Christina M. Koppin, and Mitchell E. Geffner

Abstract

Congenital adrenal hyperplasia (CAH) is a primary adrenal insufficiency and an autosomal recessive disorder that ranges in clinical severity from a classical, severe salt-wasting form to a mild, nonclassical form. In all patients, CAH involves adrenal hormone deficiencies and androgen excess. Females with CAH can have hyperandrogenism symptoms. Classical CAH presents in the newborn period with ambiguous genitalia in females and can be detected early in males with newborn screening. Clitoroplasty and vaginoplasty are surgical procedures that can correct ambiguous genitalia in females with CAH. Nonclassical CAH has a broader spectrum of clinical presentations, including premature pubarche, menstrual irregularities, and infertility. Glucocorticoid replacement therapy remains the mainstay of treatment, with the use of mineralocorticoid replacement in some classical patients and antiandrogen therapies in select female patients. Medication dosages, hormone levels, growth, and puberty need to be carefully monitored during childhood and adolescence, and hypercortisolism should be avoided in order to optimize final adult height and reduce potential morbidity. Long-term considerations of cardiovascular disease risk, bone mineral density, and fertility in adults remain under investigation.

Keywords

Congenital adrenal hyperplasia • Adrenal insufficiency • Cortisol deficiency • Cardiovascular risk • CAH • NCAH • Adolescent • Hyperandrogenism • 21-Hydroxylase deficiency • Childhood

Contents

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1 Introduction

1.1 Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that affects 1:10,000 to 1:20,000 children born worldwide (Speiser et al. 2010). CAH is a cause of primary adrenal insufficiency that results from a defect in the steroidogenic pathway, most commonly due to a mutation in the *CYP21A2* gene leading to 21-hydroxylase deficiency (21OHD) (Kim et al. 2012) present in ~95% of cases of CAH. The 11-hydroxylase deficiency (11OHD) is the next most common form present in ~5% of cases (Merke and Bornstein 2005; New et al. 2000; Kim and Donohoue 2014). Affected patients present with a spectrum of clinical severity and are classified as either severe (or classical) or late onset (or nonclassical; NCAH), depending on their specific mutations of the *CYP21A2* gene. There are 12 common mutations of the *CYP21A2* gene that can be commercially tested for as part of a screening multiplex panel, including small and large gene deletions and amino acid substitutions (Charmandari et al. 2002a). Rarer CYP21A2 mutations can be assessed by gene sequencing. This chapter will focus on patients with CAH due to 21OHD. Unless otherwise stated, CAH refers to the 21OHD form hereafter.

1.2 Classical Congenital Adrenal Hyperplasia

Patients with classical CAH have several complete or near-complete hormone deficiencies including cortisol, aldosterone, and epinephrine (Merke and Bornstein 2005; Kim et al. 2014). Affected patients also have androgen excess driven by increased ACTH levels that result from cortisol deficiency. Among patients with classical CAH, the salt-wasting (SW) form occurs in ~67% of patients and the simple-virilizing (SV) form in ~33% of patients (Merke and Bornstein 2005). Newborns and children with SW CAH suffer from near-complete aldosterone deficiency, which can result in significant salt loss from the kidneys. If left untreated, affected patients can develop salt-wasting crises which can lead to death. Patients with SV CAH maintain ~1–2% of enzyme activity and are at risk for adrenal crisis to a lesser extent than those with SW CAH (New et al. 2013). Females with either form of classical 21OHD (as well as those with 11OHD) are typically identified at birth secondary to ambiguous genitalia; however, males can take much longer to diagnose because of lack of genital ambiguity (Merke and Bornstein 2005).

To this point, newborn screening for classical CAH has altered clinical practice permitting the early identification of both male and female newborns with classical CAH (generally in the first week of life). In the USA, screening for classical CAH due to 21OHD was instituted on a state-by-state basis beginning with Alaska in 1977 (Pang et al. 1982) and in all states, Washington DC, and Guam by 2008 (Kim and Donohoue 2014).

Classical CAH is more common in certain ethnicities (most frequently in Alaskan Aleutian Yupik Eskimos) and does not commonly affect African American, Asian, and East Indian populations (Merke and Bornstein 2005; New et al. 2013). The results of ACTH stimulation testing (cosyntropin 250 mcg IV) can be used to help differentiate between classical CAH subtypes depending on the 60′ stimulated 17-OHP level. In general, SV CAH patients have stimulated 17-OHP levels of 10,000–25,000 ng/dL, whereas SW CAH patients have stimulated 17-OHP levels up to 100,000 ng/dL.

1.3 Nonclassical Congenital Adrenal Hyperplasia

21OHD is also the most common cause of NCAH, the mildest form of CAH, with an overall prevalence of 1:1000 (Finkielstain et al. 2012). Higher

rates for NCAH are seen in certain ethnic groups, including Ashkenazi Jewish (1:27), Hispanic (1:40), Yugoslav (1:50), and Italian American (1:300) populations (New 2006).

Patients with NCAH due to 21OHD maintain 20–50% of normal 21-hydroxylase activity, resulting in a milder phenotype than seen in patients with classical CAH (Witchel and Azziz 2010).

However, as a result, signs and symptoms of virilization can vary and be difficult to predict (Kashimada et al. 2008). Signs and symptoms seen in affected patients are secondary to androgen excess and can include premature pubarche, growth acceleration, and advanced bone age in growing children, along with hirsutism, acne, delayed menarche, menstrual irregularities, and infertility in adolescent and adult females (Pall et al. 2010). Symptoms typically present during adolescence, although most patients with NCAH due to 21OHD are thought to be asymptomatic and may never be diagnosed (Witchel 2013).

- If symptomatic, the clinical phenotype in females is similar to that seen in patients with polycystic ovarian syndrome (PCOS), another androgen excess disorder (Rosenfield et al. 2015). PCOS is the most common symptomatic androgen excess disorder, affecting 6–10% of reproductive-age women (Pall et al. 2010; Rosenfield et al. 2015).
- Less common effects of excess androgens that potentially may occur in patients with either NCAH due to 21OHD or PCOS include an enlarged clitoris and ovarian cysts (Kim and Donohoue 2014). NCAH due to 21OHD has been identified in 2–3% of women with hyperandrogenism (Escobar-Morreale et al. 2008; Fanta et al. 2008).

Unstimulated early morning serum 17-OHP levels in females with NCAH due to 21OHD are generally mildly elevated between 170 and 300 ng/dL (Kim and Donohoue 2014). However, patients with NCAH due to 21OHD may also have normal unstimulated 17-OHP levels, and conversely, women with PCOS may have mildly elevated 17-OHP levels (Pall et al. 2010).

- Therefore, to differentiate between these entities, ACTH stimulation testing should be employed. In patients with NCAH due to 21OHD, 60-min 17-OHP levels are generally between ~1200 and 10,000 ng/dL. Although the minimal stimulated "cutoff" level of 17-OHP has been debated, it is still much higher than the ACTH-stimulated 17-OHP level in patients with PCOS (Merke and Bornstein 2005; Kim and Donohoue 2014; Pall et al. 2010).

In addition, women with classical CAH may develop secondary PCOS (Rosenfield et al. 1994), with an increased incidence of polycystic ovaries found on ultrasound in women with CAH (Kim and Merke 2009).

2 Puberty/Adolescence

Postnatal exposure to androgen excess occurs in patients with CAH under suboptimal hormonal control. It is, therefore, vital to closely monitor the hormonal levels of patients with all forms of 21OHD to ensure proper growth and puberty.

Optimizing hormonal control can also aid in avoiding morbidity associated with the development of irregular menses, obesity, hypertension, osteoporosis, and adrenal rest tumors (Finkielstain et al. 2012). This can be particularly important during adolescence, when sex hormones, rapid growth, and transition to independence can make it challenging for teenagers to achieve good hormonal control, either because of nonadherence or unpredictable physiology. When females with classical CAH are adequately treated, many have regular menses following menarche (Premawardhana et al. 1997), although, if poorly controlled, they may have primary amenorrhea or delayed menarche (Richards et al. 1978).

Short final adult height can result from hypercortisolism and/or hyperandrogenism, with a large study in the USA noting an average loss in final adult height of -1.0 ± 1.1 SD in adults with classical CAH (-15.0 ± 16.5 cm for males and -10.8 ± 11.9 cm for females) and -0.4 ± 0.9 SD in adults with NCAH (-6.0 ± 13.5 cm for males

and −4.3 ± 9.7 cm for females) (Finkielstain et al. 2012). Another pediatric study showed similar results, with final adult height ~10 cm below the midparental height (Lin-Su et al. 2011), and a large adult study in the UK noted an average height loss in males with classical CAH of 10.4 cm and 6.4 cm in women (Han et al. 2014). Secondary to androgen excess, children with classical CAH can develop premature pubarche/adrenarche, manifested by early-onset pubic and/or axillary hair, acne, undue bone age advancement, and accelerated growth, with secondary central precocious puberty (breast development < 8 years in girls and testicular development < 9 years in boys) in some severe cases. Thus, all children with classical CAH need to be monitored clinically for signs of early puberty, an unexpected increase in growth rate, and bone age advancement on x-ray, as these complications can negatively impact final adult height. Youth with NCAH can also develop these complications and should be monitored for abnormal growth and puberty (Witchel 2013).

3 Medical Management

3.1 Daily Medication Management

The clinical management of CAH focuses on two main goals: replacement of hormone deficiencies and suppression of androgen excess. The mainstay of treatment in children is glucocorticoid (GC) replacement with hydrocortisone. For patients with the salt-wasting form of CAH, and some patients with simple-virilizing form, daily fludrocortisone replacement is necessary to correct real or subclinical mineralocorticoid (aldosterone) deficiency. Physiological studies have shown that the secretion rates of aldosterone remain constant throughout life in normal individuals (Weldon et al. 1967). In patients with CAH, the recommended dosing of fludrocortisone is also relatively constant at 0.05–0.2 mg/day, divided into once- or twice-daily doses (Speiser et al. 2010). From infancy until approximately 1 year of age, sodium chloride supplementation of 1–2 gm/day or 4 mEq/kg/day divided into four daily doses and given along with feedings is also recommended, as breast milk and formula contain inadequate amounts of sodium to protect against salt wasting in infants with CAH secondary to 21OHD (Mullis et al. 1990). Routine laboratory testing of electrolyte levels and plasma renin activity can help guide fludrocortisone and sodium chloride dosing.

To assess the efficacy of GC replacement, measurement of serum steroids should always be undertaken at the same time of day and with the same duration of the time from the last dose of medication (e.g., immediately before the morning hydrocortisone dose at 7 AM, 8 h after the bedtime dose of hydrocortisone at 11 PM). This standardization of testing conditions is critical to allow comparisons to previous laboratory values for accurate monitoring (Merke and Bornstein 2005; Merke and Poppas 2013). Care must be taken to avoid overtreatment with GC, in an attempt to suppress excess androgen levels, as this could lead to deleterious effects on multiple organ systems. The balancing act between controlling hyperandrogenism and avoiding hypercortisolism remains a challenge for clinicians and demands regular follow-up care. Routine laboratory monitoring of serum steroids, typically including 17-OHP, androstenedione, and/or testosterone, every 3–6 months is used to assess efficacy of GC dosing (Speiser et al. 2010).

Appropriate dosing is also critical to avoid the risk of adrenal crisis and accelerated growth plate maturation and closure from adrenal androgen excess as a result of undertreatment while also avoiding the consequences of iatrogenic Cushing syndrome with overtreatment.

Radiography of the left wrist for bone age evaluation should be done semiannually or annually, after the age of 2 years, to detect undue advancement in bone age compared to chronological age, which, if present, would be a marker of chronic poor disease control (Speiser et al. 2010).

For the growing child with CAH, hydrocortisone tablets are the most appropriate GC medication to replace deficient cortisol and to thereby suppress ACTH and adrenal androgen production.

- Hydrocortisone dosing of 10–15 mg/m^2/day is typically divided into three daily doses, although more frequent dosing might be

necessary in some patients to achieve hormonal control. A large dose in the evening/bedtime is used in patients with CAH to suppress the early-morning surge of ACTH and subsequent peak androgen overproduction by morning (Merke and Poppas 2013), with the next highest dose given in the morning, in concordance with the AM cortisol surge. In adults, a larger hydrocortisone dose at bedtime may not be feasible secondary to sleep problems, so an alternative is to give the highest dose in the morning, mimicking the diurnal pattern of cortisol production; in children, either dosing pattern did not differ in sleep activity or disease control (German et al. 2008).

- For postpubertal adolescent patients who have nearly or completely finished their linear growth, a longer-acting GC can be used for more convenient once- or twice-daily dosing. Liquid formulations, such as prednisolone suspension or dexamethasone elixir, also allow for greater fine-tuning of the daily dose. Recommended dosing, in terms of hydrocortisone equivalents, remains 10–15 mg/m^2/day (Speiser et al. 2010).

The relative potency of long-acting GC medications varies among subjects depending on pharmacokinetic metabolism. Therefore, similar to hydrocortisone, dose titration should be based on laboratory monitoring and symptoms (Speiser et al. 2010), with the goal of providing the smallest GC dose in order to effectively replace the GC deficiency and suppress adrenal androgens and thereby avoid associated comorbidities, such as short final adult height. During adolescence, potentially adverse effects of GCs on final adult height can be reduced if the hydrocortisone equivalent dosing is less than 17 mg/m^2/day (Bonfig et al. 2009).

3.2 Sick Day Management

The normal physiological response to acute illness or trauma involves a coordinated neuroendocrine mechanism, including increases in stress hormones: epinephrine, cortisol, and growth hormone. The rise in counter-regulatory hormone levels protects against hypoglycemia via gluconeogenesis and glycogenolysis (Kim et al. 2014).

In patients with CAH, additional GC medication, often referred to as a "stress dose," must be given promptly to mimic the physiological cortisol stress response and avoid adrenal crisis during acute illness or trauma. Situations requiring a stress dose include fever $\geq$ 100.4°F, vomiting, diarrhea, and physical trauma (i.e., broken bone or concussion).

- The daily oral maintenance dose of GC is increased for moderate or severe illness, with ~25–30 mg/m2/day of hydrocortisone or its equivalent for moderate illness and 50 mg/m2/day (divided into Q6 hour dosing) during times of severe illness.
- If there is vomiting shortly after an oral stress dose, the oral stress dose should be repeated.
- Small frequent sips of clear fluids containing glucose are recommended for illnesses with vomiting and/or diarrhea. In situations where oral stress dosing is not possible (i.e., repetitive vomiting within 30 min, loss of consciousness, seizures, etc.), hydrocortisone should be administered via an intramuscular (IM) injection without delay.

Caregivers should be trained to recognize situations when IM hydrocortisone is indicated and be able to administer this injection to their child (or to themselves beginning in young adulthood). An emergency hydrocortisone injection kit with medication, sterile saline solution, and injection supplies (hypodermic needle, alcohol wipes, and band aids) should be easily accessible or carried with the patient at all times for emergency use. Combination medication storage devices, such as the Act-O-Vial® kit, allow for the rapid mixing of hydrocortisone powder with sterile injection solution and reduce dilution steps required to administer the injection.

- Simple age-based dosing guidelines for IM hydrocortisone are 25 mg for infants and toddlers, 50 mg for children, and 100 mg for adolescents/adults (Speiser et al. 2010).

A medical identification bracelet/necklace and/or wallet card stating that the patient has "adrenal insufficiency and needs hydrocortisone," along with an emergency letter, is recommended for reference by first responders and/or paramedics in case of a medical emergency such as a motor vehicle accident. The rapid identification of patients with adrenal insufficiency would enable the administration in the field of an emergency stress dose of hydrocortisone in order to mimic the physiological stress response to illness or trauma. Injection of hydrocortisone should be given in a timely fashion and not be delayed until presentation at the emergency department.

3.3 Other Medications

To counteract adverse effects of hyperandrogenism, such as hirsutism, in adolescent and adult females, adjunctive therapies can be considered, including oral contraceptive pills (OCPs) and spironolactone. OCPs suppress ovarian androgen production and increase the level of sex hormone-binding globulin (SHBG), which also reduces the serum concentration of free testosterone (Merke and Poppas 2013).

OCPs containing antiandrogens such as drospirenone or cyproterone (not available in the USA) may prove to be more effective in combating manifestations of hyperandrogenism in these young women (Matthews and Cheetham 2013). Spironolactone has antiandrogenic effects that can aid in the reduction of hirsutism and acne. However, its use may require an increase in the mineralocorticoid replacement medication, fludrocortisone, in classical CAH patients (Auchus and Arlt 2013).

Another nonsteroidal antiandrogen medication, flutamide, has been used to treat patients with PCOS and has been used in an off-label manner in patients with classical CAH (Auchus and Arlt 2013). Flutamide has been studied experimentally in combination with an aromatase inhibitor in children with CAH, helping to maintain normal growth velocity and bone maturation (Merke et al. 2000; Hero et al. 2005).

Although not standard of care, gonadotropin-releasing hormone (GnRH) analog therapy (i.e., leuprolide or histrelin) has been utilized clinically for children with CAH who exhibit central precocious puberty to temporarily halt pubertal progression and thereby preserve final adult height. Otherwise, short final adult height can result from early growth plate closure resulting from either poor hormonal control and/or overtreatment with GC (Han et al. 2014). In some cases, growth hormone injections have been used off-label to increase height velocity in combination with a GnRH analog to slow central puberty and growth plate closure associated with advanced bone age (Quintos et al. 2001).

3.4 Multidisciplinary Team Approach and Transition to Adult Care

Coordination of care and communication between primary care provider and subspecialty team members, including endocrinologist, urologist, and gynecologist, is crucial to ensure optimal treatment of the patient with CAH. The multidisciplinary team approach includes collaboration with psychosocial services to address potential psychological distress in both the patient and parents (Auchus et al. 2010). Routine assessment of quality of life by providers is encouraged to determine the impact of medical management and surgical interventions pertaining to CAH-related care (Speiser et al. 2010).

The transition to adult care should be initiated by conversations with parents and patient during early adolescence and progress throughout the teenage years to include a written plan that increases self-care responsibilities for the patient and identifies adult providers in a new medical home (Cooley and Sagerman 2011).

Ideally, specialty clinics jointly staffed by pediatric, reproductive, and adult endocrinologists, along with gynecologists and urologists, can ease the transition to adult care and conveniently allow for multiple providers to see the patient at the same clinical encounter. Specifically, adolescent girls with CAH with virilization require consultation with a gynecologist prior to and/or during early puberty. An examination under anesthesia is

recommended, and joint examination with an experienced pediatric urologist is also recommended (Speiser et al. 2010). Discussion with the patient and family about potential issues related to sexual activity should be discussed with the patient and family regarding the possible need for surgical intervention. This topic will be discussed further in the section on "Surgical Considerations."

3.5 Fertility and CAH

Fertility rates in CAH women have been reported as reduced despite normal pregnancy rates (Casteras et al. 2009). However, lower pregnancy rates have also been found in CAH women compared to controls (Helleday et al. 1993) with elevated progesterone postulated as a potential etiology. The pregnancy rates may remain low despite the addition of fertility treatments (Hagenfeldt et al. 2008). In women with NCAH who are untreated, the fertility rate has been reported to be 50% (Feldman et al. 1992). CAH males who develop testicular adrenal rest tumors (TART) may experience testicular damage leading to infertility in adulthood (Claahsen-van der Grinten et al. 2009). This topic will be further discussed in the following section on "Comorbidities."

4 Comorbidities in CAH

4.1 Bone Mineral Density

Lifelong GC therapy in patients with CAH has the dual goals of physiological hormone replacement and suppression of excess adrenal androgens. However, if not titrated properly, long-term therapy could lead to concerns for secondary osteopenia and osteoporosis in adulthood.

Mechanistically, GCs both suppress osteoblast activity and promote osteoclast activity, lead to early epiphyseal closure, and blunt the GH-IGF-I axis (Hofbauer et al. 1999; Falhammar et al. 2007). Studies are inconsistent in showing lower bone mineral density in patients with CAH compared to controls, and the risk of osteoporosis-related fractures in CAH seems to be equivocal in premenopausal women (Falhammar et al. 2007; Sciannamblo et al. 2006; Koetz et al. 2012). It has been hypothesized that the ill effects of chronic, supraphysiological GC therapy are counteracted by elevated androgen levels in patients with CAH. These androgens in turn are converted to estrogens, which are known to inhibit osteoclast bone resorption (Lin-Su and New 2007). Thus, the goal of daily GC medication dosing should focus on using the minimum effective GC dose to appropriately lower 17-OHP and androgen levels as high total cumulative and average daily GC doses have been associated with decreased bone mineral density in patients with CAH (Chakhtoura et al. 2008).

Individuals with CAH have been found to have rates of vitamin D deficiency and insufficiency consistent with those in the general population (Finkielstain et al. 2012; Looker et al. 2011). With this in mind, regular physical activity and calcium and vitamin D supplementation are recommended for osteoporosis prevention beginning in adolescence.

4.2 Adrenal Rest Tumors

Poor control of CAH, especially cases requiring adrenalectomy, can lead to the development of adrenal rest tumors in gonadal tissue due to hypersecretion of ACTH and the expression of ACTH-specific receptors on the adrenal tissue in the testes (TARTs) or ovaries (OARTs) (King et al. 2009). TARTs have been observed more frequently in the testicles of male patients with poorly controlled CAH (Claahsen-van der Grinten et al. 2009). More recently, case studies have reported on the presence of OART in female CAH patients with poor disease control (Tiosano et al. 2010; Thomas et al. 2013). The prevalence of OART is rare with less than two dozen case reports in the literature, which is far less common than the male counterpart phenomenon of TART that has been observed to occur in up to 95% of male CAH patients, especially with increasing age and/or poor CAH control (Finkielstain et al. 2012; Zaarour et al. 2014; Mouritsen et al. 2010; Arlt et al. 2010).

Of note, more advanced imaging techniques such as PET/CT scans have been shown to visualize OART tissue when the first-line ultrasound modality does not detect abnormalities (Crocker et al. 2012). Regardless, adrenal rest tumors in either the testis or ovary can potentially interfere with the reproductive function of these organs, including menstrual cycles, and, in the worst case, lead to secondary infertility (Claahsen-van der Grinten et al. 2009; Thomas et al. 2013).

In terms of screening, it is recommended for males to be screened for TARTs starting no later than adolescence (Speiser et al. 2010) although recommendations vary depending on the group and include screening children (Finkielstain et al. 2012; Claahsen-van der Grinten et al. 2009). It is recommended that transabdominal and pelvic ultrasounds be conducted to evaluate the ovaries for cysts and adrenal rest tumors in females with CAH where ovarian dysfunction is suspected (Zaarour et al. 2014).

4.3 Cardiovascular Disease Risk Factors

Increased cardiovascular disease (CVD) risk factors are commonly seen in adults (Falhammar et al. 2015) and children (Finkielstain et al. 2012; Falhammar et al. 2015; Subbarayan et al. 2014) with classical CAH secondary to 21OHD, including abnormal cholesterol fractions, insulin resistance, obesity, and hypertension. Across various studies, there are mixed reports of associations with glucocorticoid and mineralocorticoid replacement therapies.

Childhood obesity rates in CAH exceed the high/epidemic rates seen in unaffected normal children in the USA and several other developed countries (Finkielstain et al. 2012; Subbarayan et al. 2014; Volkl et al. 2006; Cornean et al. 1998). Obesity is an important cardiovascular disease risk factor, making it a concerning complication facing youth and adults with CAH. The etiology for obesity in CAH is not entirely clear; hyperandrogenism, lifelong glucocorticoid treatment, and hormonal imbalances inherent in classical CAH are potential contributing factors (Finkielstain et al. 2012; Kim and Merke 2009; Arlt et al. 2010). Abnormally elevated leptin levels in CAH individuals could also be an important factor, as otherwise healthy obese individuals also exhibit elevated leptin (Charmandari et al. 2002b).

Increases in fat mass measured by different techniques such as simple skinfold thickness, bioelectrical impedance analysis, and whole-body dual-energy x-ray absorptiometry are concerning (Cornean et al. 1998; Isguven et al. 2008; Stikkelbroeck et al. 2003). As well, abdominal adiposity has been shown to be increased in adolescents and young adults with classical CAH due to 21-hydroxylase deficiency, using single-slice computed tomography (Kim et al. 2015). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are both increased in CAH, with a higher proportion of pro-inflammatory VAT than SAT, than was seen in matched controls. VAT in particular is strongly associated with metabolic syndrome and cardiovascular disease, and this unfavorable abdominal fat distribution (for the same degree of obesity) is particularly concerning. In adolescents and young adults with CAH, VAT and SAT strongly correlated with measures of obesity such as the waist-to-height ratio and fat mass. As well, there were strong correlations between abdominal adiposity and inflammatory markers [plasma activator inhibitor-1 antigen (PAI-1), highly sensitive C-reactive protein (hs-CRP), and leptin], low-density lipoprotein cholesterol (LDL), and homeostasis model assessment-estimated insulin resistance index (HOMA-IR). Interestingly, no sex differences were noted for either VAT or SAT in individuals with CAH.

There is evidence for insulin resistance in children and adolescents with classical CAH (Finkielstain et al. 2012, Charmandari et al. 2002b; Sartorato et al. 2007; Williams et al. 2010) using either HOMA-IR or oral glucose tolerance testing. Hyperandrogenism itself may contribute to hyperinsulinism, as studied in adolescent and adult females without CAH (Kim and Merke 2009), which could potentially translate to the hyperandrogenic cohort of females with CAH. The epinephrine deficiency seen in patients with classical CAH, secondary to impaired adrenomedullary development, has been associated

with elevated insulin and leptin levels and may contribute to insulin resistance (Kim and Merke 2009; Charmandari et al. 2002b).

High blood pressure is commonly seen in children. Potential etiologies that have been studied include changes in mineralocorticoid sensitivity in infants contributing to transient hypertension, excessive GC and/or fludrocortisone dosages, and obesity. Fludrocortisone dosages are relatively larger for body size at younger ages, although the dose does not tend to correlate with blood pressure. Overall, elevated BMI or obesity has not been associated with hypertension in CAH children (Finkielstain et al. 2012; Bonfig and Schwarz 2014; Nebesio and Eugster 2006). Hypertension, or higher blood pressure compared to controls, has recently become more commonly observed in adults with classical CAH (Finkielstain et al. 2012; Arlt et al. 2010; Subbarayan et al. 2014; Mooij et al. 2011).

Carotid intima media thickness (CIMT), a marker of subclinical atherosclerosis, has been found to be greater in young adult with CAH than in matched controls (Sartorato et al. 2007). These differences are not observed in children and adolescents with CAH (Harrington et al. 2012; Amr et al. 2014; Kim et al. 2016). However, a study looking at subgroups of CAH adolescents with poorly controlled disease found correlations between chronic hyperandrogenism and increased CIMT (Kim et al. 2016). These findings are consistent with the detection of increased CIMT in women with PCOS compared to controls (Meyer et al. 2012) and the increased CIMT seen in adult males compared to adult females. Adult women without CAH have later CVD manifestations than adult men, beginning in middle-to-late adulthood (Mendis et al. 2011). Maintaining good hormonal control is, therefore, potentially important in preventing the development of this CVD risk factor in patients with CAH, a population already predisposed to obesity, hypertension, and insulin resistance.

5 Surgical Considerations

The mutation in 21-hydroxylase results in excess androgen exposure beginning in utero during critical developmental periods and results in variable degrees of virilization of the external genitalia of newborn girls, including characteristics of clitoromegaly, fused labia majora, and a common urogenital sinus (Kim and Donohoue 2014). The Prader scale is used to describe the degree of virilization (Fig. 1).

The presentation of ambiguous genitalia at birth should raise suspicion for the diagnosis of a female with CAH secondary to 21OHD, in particular if there is a male-appearing child with bilateral cryptorchidism.

Although the external genitalia can be partially or even fully male appearing (without palpable testes) in patients with CAH, the internal female reproductive structures (ovaries, fallopian tubes, uterus, and proximal vagina) in girls are unaffected and have the potential to function normally in regard to menstruation and pregnancy later in life.

Of note, the external genitalia of newborn male infants with CAH are normal, notwithstanding the presence of hyperpigmentation, and are not adversely affected by the excess androgen exposure in utero. Historically, this often resulted in a

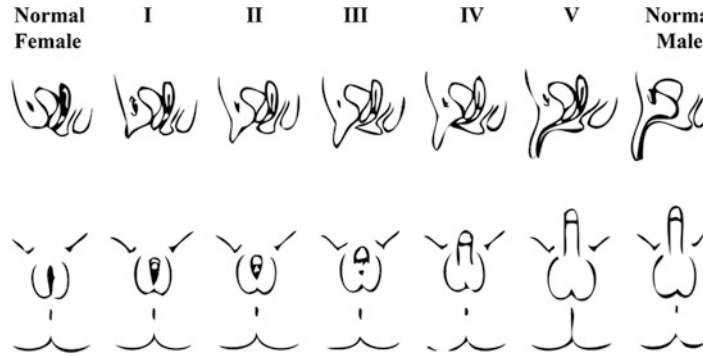

Fig. 1 Prader scale for ambiguous genitalia in females (Adapted from Prader and Gurtner 1955)

delayed diagnosis of CAH, with the male patient presenting with early adrenal crisis or later with precocious pubarche, rapid growth, and advanced bone age. With the implementation of newborn screening for CAH, this presentation should rarely if ever occur.

Surgical considerations for females with CAH have been a debated topic in regard to the extent of procedures to be performed and the age at which to perform them. Regardless of these debates, prior to any consideration of surgery, it is critical that the patient is medically stable; that the caregivers are fully informed and understand the indications, risks, benefits, and alternatives to the procedures; and that an experienced pediatric urologist (or pediatric surgeon with significant experience in these specific procedures) performs the planned surgery (Auchus et al. 2010). Also critical is the support of experienced pediatric endocrinologists, anesthesiologists, and social workers.

Androgen exposure causes enlargement/elongation of the clitoris, regression of distal vaginal/introital structures, fusion of the labia majora, and progressive tubularization of the urethra/common genitourinary sinus tissue.

In the past, CAH females with virilization would often undergo a feminizing genitoplasty procedure early in life. In fact, the American Academy of Pediatrics still generally recommends that genital surgery be performed in the first 15–18 months of life, prior to development of genital awareness (Hughes et al. 2006). Depending on the degree of virilization and level of the vaginal confluence, reconstructive procedures may include vaginoplasty, labioplasty, and/or clitoroplasty. However, some believe that vaginoplasty during infancy carries higher risks of vaginal stenosis requiring dilation or surgical revision later in life (Speiser et al. 2010). There is no precise objective criterion for when a clitoroplasty should be performed. Should a clitoroplasty be done, care must be taken during the dissection to preserve the clitoral head and neurovascular bundles to maintain sensation (Lee and Witchel 2002). Benefits of early vaginoplasty may include a reduction in the risk of urinary tract infections (primarily in those with a significant common urogenital sinus); shorter surgical distances; elastic tissues; improved wound healing, creating a functional vaginal opening to allow for menstrual flow; and early attainment of normal-appearing external genitalia prior to genital awareness. It may promote normal patient psychosexual development and social acceptance, as well as alleviate parental distress (Speiser et al. 2010). Procedures performed during infancy (prior to 12 months of age) benefit from the presence of more elastic vaginal tissue related to elevated estrogen levels. These estrogen levels are a result of the "mini-puberty of infancy," a physiological activation of the hypothalamic-pituitary-gonadal axis that begins in the first month of life and wanes to prepubescent levels over the first 2 years for females (Kuiri-Hanninen et al. 2014).

The most current consensus statement for the care of patients with virilizing CAH recommends vaginoplasty be performed using a urogenital mobilization approach prior to 12 months of age for patients with significant virilization (Prader score $\geq$3) (Speiser et al. 2010).

Vaginoplasty can in some cases be performed before age 6 months by an experienced pediatric urologist when the child is suffering from recurrent urinary tract infections (Auchus et al. 2010). A partial urogenital mobilization (PUM) or limited proximal dissection is generally preferred over a total urogenital mobilization (TUM) procedure, which involves proximal dissection deep to the urogenital diaphragm, because of concerns about disruption of important urethral muscular and support structures involved in urinary continence.

The PUM or limited proximal dissection procedure was described in detail by Rink et al. (2006) and has been reported to produce cosmetic and urinary functional outcomes in most cases of females with virilization from CAH while potentially reducing morbidity in comparison to the more extensive TUM procedure. The PUM procedure has reported advantages of an increased likelihood of preserving clitoral innervation,

avoidance of dissection of supportive tissues around the bladder neck, and reduction of vaginal foreshortening compared to the TUM procedure (Rink et al. 2006). In some cases, however, the PUM procedure may need to be converted to a TUM procedure if the vagina remains a significant distance from the perineum after PUM.

Caregivers may decide to delay vaginoplasty for the female CAH patient who does not have significant virilization (i.e., Prader score <3). The potential benefits of delaying surgery until the patient has reached puberty may include a reduced risk of developing vaginal stenosis and the associated need for dilation therapy or surgical revision (Speiser et al. 2010). Choosing to delay surgery until puberty also allows the patient to take part in the decision-making and has the advantage of more elastic vaginal tissue associated with elevated estrogen levels during adolescent puberty. Conversely, delayed reconstructive surgery results in greater distances from the perineum to the vagina and carries higher risks of wound infection/wound-healing issues due to local colonization of mature hair follicles. Emotional distress can also be a significant issue for surgical patients when extensive external anatomical changes and gender role changes are required (Woelfle et al. 2002). The typical technique used is the Fortunoff posterior flap vaginoplasty, which is indicated if the entry point of the vagina into the common urogenital sinus is low, as is often the case with Prader score of <3 (Schaeffer et al. 2010). Long-term studies with standardized outcome measures are needed to investigate whether early vaginoplasty during infancy or a delayed vaginoplasty during adolescence leads to more favorable outcomes regarding urinary continence, rate of urinary tract infections, sexual and reproductive function, and psychological outcomes.

If indicated, clitoroplasty should be performed concurrently with vaginoplasty during infancy or adolescence. Reduction clitoroplasty has been the most commonly performed procedure for clitoromegaly associated with CAH (Poppas et al. 2007). A dorsal nerve-sparing technique for the reduction clitoroplasty procedure to preserve innervation of the glans clitoris and future sexual function has been described, involving excision of corpora cavernosa tissue at a starting point that is 1.5–2 cm distal to the bifurcation allowing for elevation and support of the glans clitoris and preserving clitoral erection during arousal (Poppas et al. 2007). Initial studies on clitoral viability and sensitivity outcomes after clitoroplasty show preservation of vascular blood flow and sensitivity following the dorsal nerve-sparing clitoroplasty (Yang et al. 2007). However, long-term follow-up on sexual function outcomes are still lacking.

Some may consider the clitoroplasty procedure as a cosmetic procedure and not medically necessary, as it does not reduce morbidity in the same way that vaginoplasty can allow for normal menstrual flow and sexual function, and reduce the risk for frequent urinary tract infections. However, others strongly argue that the procedure is necessary for the appropriate psychosocial development of the child and to avoid significant distress caused by having different-appearing genitalia (Speiser et al. 2010). Therefore, caregivers must be fully informed and demonstrate understanding of the indications, benefits, risks, and alternatives for the procedure prior to electing to have their child undergo a clitoroplasty. Whether caregivers choose to pursue a clitoroplasty for their child at the time of vaginoplasty, or elect not to have the clitoroplasty done, providers should be supportive of the decision and provide follow-up consultation as needed.

6 Conclusion

There is a wide spectrum of clinical phenotypes in CAH and morbidity related to both hormone deficiencies and androgen excess inherent to the condition. Adolescents with CAH need to be monitored carefully for proper growth and pubertal development to optimize final adult height and avoid other comorbidities.

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7 Cross-References

- Hyperandrogenism: Acne and Hirsutism
- Treatment of Gynecological Congenital Anomalies
- Workup and Management of Polycystic Ovary Syndrome

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