4.04 Hypothalamic–Pituitary–Adrenal Axis: Congenital Adrenal Hyperplasia

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4.04.1 Introduction

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders characterized by defective adrenal steroid biosynthesis. The conversion of precursors to cortisol and aldosterone in the zona fasciculata and zona glomerulosa of the adrenal cortex occurs in several major enzyme-mediated steps. Deficiency in any one of these enzymes may result in impairments of glucocorticoid, mineralocorticoid, and/or sex hormone production. CAH affects 1/10 000 to 1/15 000 live births, depending on the specifics of the enzyme dysfunction. Clinical presentation of the five different forms of CAH results from various unique combinations of elevated or deficient hormone precursors and products. The most common enzyme defect is 21-hydroxylase deficiency (21OHD), which accounts for more than 90% of cases and results in cortisol deficiency, chronically elevated ACTH, and overproduction of cortisol precursors that are instead peripherally converted to testosterone. In the classical form, 21OHD CAH often presents at birth with ambiguous genitalia in affected females, while the primary indication in affected newborn males is salt loss, which can be life-threatening. Nonclassical 21OHD (NC-21OHD), with presentation in early/late childhood or adolescence, may be characterized by rapid growth and pubertal-like development, such as genital virilization in males or early pubic hair growth in females. In adolescence, affected females may also present with a syndrome of hirsutism, acne, and disrupted menses. One challenge of treatment lies in the balance of glucocorticoid and mineralocorticoid replacement and avoidance of treatment-related complications, such as growth suppression, obesity, and/or adverse metabolic profiles in adulthood. Serum 17OH-progesterone and adrenal androgens (in females), which are elevated in 21OHD CAH due to enzymatic deficiency, may serve as markers for monitoring hormone replacement treatment. Historically, surgical interventions have been advised to correct genital malformations in females at around 12–18 months; however, current practices are more likely to recommend deferring any cosmetic repairs until the affected individual is able to consent to such treatment.

4.04.2 Epidemiology

Data based on ~6.5 million newborn infants from screening programs in several Western countries indicate that the classical form of 21OHD CAH has an incidence of 1/15 000 live births (Nordenström et al., 2005; Pang and Shook, 1997; Van Der Kamp and Wit, 2004). The United Kingdom is unique among its peers in that it does not currently include CAH as a component in the neonatal screening program (Hird et al., 2013), and the incidence there is approximately 1/12 000 based on clinical case ascertainment. In ~75% of cases of classical 21OHD CAH, there is also a disturbance in mineralocorticoid regulation and associated salt loss, while non-salt-losing 21OHD CAH accounts for about 25% of cases (Therrell et al., 1998). Mild or late-onset NC CAH, is more common, with certain ethnic groups presenting with rates as high as 1/27 (Pang et al., 1988; Speiser et al., 1985). The second most common cause of CAH, 11β-hydroxylase deficiency, accounts for 5–8% of cases and occurs in about 1/100 000 live births (Nimkarn and New, 2008; Zachmann et al., 1983).

Neonatal screening has been recommended as part of clinical guidance for CAH (Speiser et al., 2010) to decrease time to diagnosis and to reduce morbidity and mortality (Balsamo et al., 1996; Brosnan et al., 1999). Given an expected 1:1 female to male ratio for autosomal recessive disorders in general, the historical female > male ratio in CAH suggested that many males may have died before a diagnosis was made. Since the advent of screening the ratio has normalized, providing indirect support for the hypothesis. However, a population-based cohort study of patients, born between 1915 and 2011 in Sweden, has shown that equal numbers of male and female babies with the severe form of the disorder were missed prior to screening, suggesting that neonatal screening improves survival in both sexes (Gidlöf et al., 2013).

4.04.3 Genetics

The gene which encodes 21-hydroxylase is a microsomal cytochrome P450 termed cytochrome P450, family 21, subfamily A, polypeptide 21, or *CYP21A2*. The gene is located on chromosome 6p21.3 within the human leukocyte antigen histocompatibility (HLA) complex (Dupont et al., 1977). Due to an autosomal recessive pattern of inheritance, expression of CAH due to *CYP21A2* mutation occurs when both inherited alleles are defective. Approximately 90% of mutant alleles are caused by recombinations between an active gene *CYP21A2* (*CYP21B*) and a pseudogene *CYP21A1P* (*CYP21A*, CYP21P) formed by the process of ancestral duplication. In this gene conversion, where deleterious material from the pseudogene is transferred to the active gene, the active gene can no longer code for functional enzymatic function (Kawaguchi et al., 1992). Around 1–2% of alterations in alleles occur spontaneously (Tusie-Luna and White, 1995). Mutations in *CYP21A2* may result in varying degrees of 21-hydroxylase activity disruption and subsequently varied degrees of disease severity (Speiser et al., 1992; Wajnrajch et al., 2001).

Most cases of 21OHD CAH are compound heterozygotes, with two different mutations in the two alleles, and phenotypic expression is typically related to the less severely compromised allele and residual 21-hydroxylase activity (Speiser et al., 1992). *In vitro* studies in a small number of mutations have revealed a correlation in the degree of disease severity and the degree of functional loss of 21-hydroxylase (Soardi et al., 2008; Tardy et al., 2010). However, a study of 1507 families with CAH owing to 21-hydroxylase deficiency found that the close genotype–phenotype relationship was more reliably observed in the salt-wasting (SW) form of the disorder. Those with the simple-virilizing (SV) variant of 21OHD CAH showed wide phenotypic variability (New et al., 2013b). Given the implications for disease severity and symptomatology, such findings should provide guidance for physicians in prenatal diagnosis and for genetic counseling with parents who are at risk of having a child with 21OHD CAH. Heterozygotes or carriers for *CYP21* mutations may also show subtle steroid biosynthesis abnormalities. In comparison to healthy controls, 50–80% of carriers show increased cortisol precursors, such as 17-hydroxyprogesterone (17-OHP), after corticotropin stimulation (Peter et al., 1990). Further effects evident in carriers include higher mean and free testosterone concentrations (Knochenhauer et al., 1997) and lower mean 24 h urinary excretion of cortisol (Charmandari et al., 2004), though there is no evidence to suggest hyperandrogenic symptoms or disorders of puberty or growth.

4.04.4 Pathophysiology

Adrenal steroid production occurs in three major pathways within the hypothalamic–pituitary–adrenal (HPA) axis. Within the adrenal, the zona glomerulosa, zona fasciculata, and zona reticularis act as separate glands producing glucocorticoids, mineralocorticoids, and sex hormones (Ganong, 1963; Guillemin and Schally, 1963), as depicted in **Figure 1**. Hypothalamic corticotropin-releasing hormone (CRH) regulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, thereby activating the HPA axis and glucocorticoid release. This HPA feedback system is mediated via the circulating level of plasma cortisol in negative feedback on CRH and ACTH. Therefore, in 21OHD, the inhibited cortisol production leads to increased ACTH production, which in turn stimulates excessive synthesis of adrenal products in pathways unimpaired by enzymatic deficiency as well as buildup of precursors, mainly 17-OHP in pathways blocked by the enzymatic deficiency (Azziz et al., 1990; White and Speiser, 2000). The accumulation of 17-OHP due to chronic elevation of ACTH leads to excess production of adrenal androgens which are converted to testosterone in the liver. However, because 21-hydroxylase deficiency is variable depending on the nature of the genetic mutation, and because minimal activity is required in the mineralocorticoid pathway, salt loss associated with mineralocorticoid deficiency usually only results in the more severe form of the condition (New et al., 2013c).

4.04.5 Clinical Features

Approximately 95% of CAH cases are due 21-hydroxylase deficiency, with about 5% of cases attributable to defects in

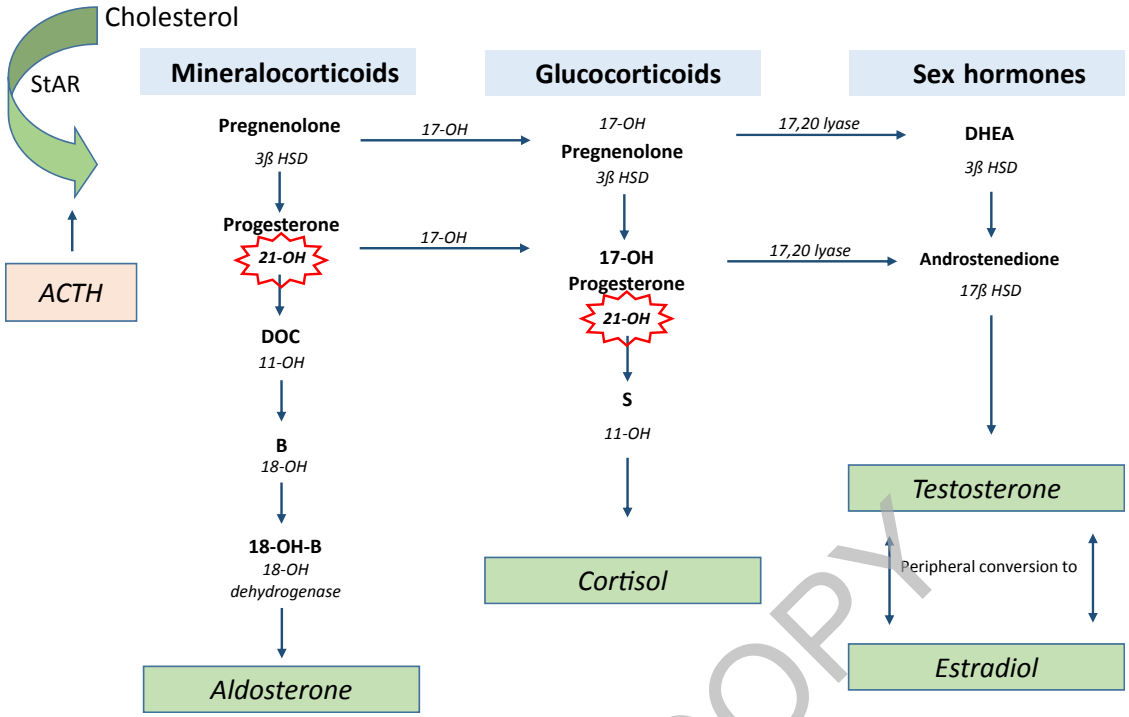

Figure 1 Adrenal steroidogenic pathways, highlighting enzymatic 21-hydroxylase deficiency (21OHD).

production of 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase/17,20-lyase, or steroidogenic acute regulatory (StAR) protein (Benkert et al., 2015; Guenego et al., 2015; Kim, 2015). The clinical symptoms of the five forms of CAH result from hormonal deficiencies and excesses, depending on the specific enzyme that is affected and the degree to which is has been compromised (see Table 1). CAH due to deficiencies of enzymes other than 21-hydroxylase presents similar clinical challenges, though these forms may involve mineralocorticoid excess or sex steroid deficiency. NC-21OHD CAH involves only mild enzyme deficiency, with effects that may compound over a period of a few years before they are noticed, i.e., from childhood onward (Beeresh et al., 2015).

4.04.5.1 Virilizing Forms of CAH (Classical 21OHD, SW/SV, and 11β-OH Deficiency)

4.04.5.1.1 External Genitalia

Because adrenocortical function begins around week 7 of gestation and sexual differentiation occurs between weeks 9 and 15, a fetus with virilizing 21OHD will be exposed to adrenal androgens during a critical window for sexual differentiation (Goto et al., 2006). As the androgens interact with androgen receptors present in genital skin, they induce changes in female external genitalia, including enlargement of the clitoris, fusion of the labial folds, and rostral migration of the urethral/vaginal perineal orifice. Genital virilization may range from mildly ambiguous to completely male in appearance. The Prader scale (Prader and Gurtner, 1955)

Table 1 Five subtypes of congenital adrenal hyperplasia (CAH) according to enzyme dysfunction

Common medical term	*Affected enzyme*	*Substrate*	*Product*	*Mineralocorticoids*	*Androgens*
21-Hydroxylase CAH	P450c21	17OH-progesterone Progesterone	11-Deoxycortisol Deoxycorticosterone (DOC)	Deficiency	Excess
11β-Hydroxylase CAH	P450c11β	11-Deoxycortisol DOC	Cortisol Corticosterone	Excess	Excess
3β-HSD CAH	3β-HSD II	Pregnenolone 17OH-pregnenolone DHEA	Progesterone 17OH-progesterone Androstenedione	Deficiency	Deficiency
17α-Hydroxylase CAH	P450c17	Pregnenolone Progesterone 17OH-pregnenolone	17OH-pregnenolone 17OH-progesterone DHEA	Excess	Deficiency
Lipoid CAH	StAR	Cholesterol	Mediates cholesterol transport across mitochondrial membrane	Deficiency	Deficiency

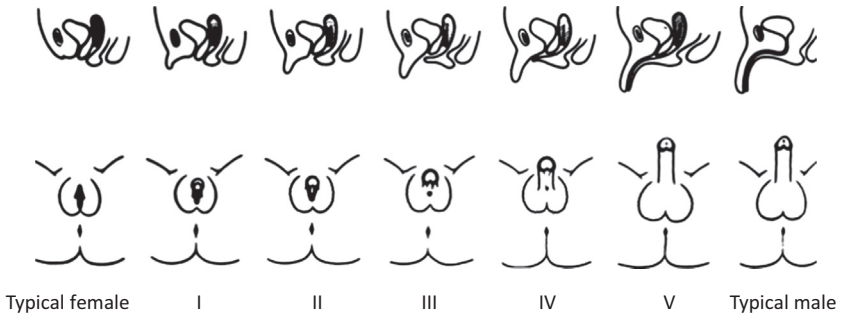

Figure 2 Scale depicting gradations in external genital virilization developed by Prader and Gurtner (1955).

is often used to classify the degree of virilization, with five stages in between normal female and normal male, noting both clitoral enlargement and labial fusion, as shown in Figure 2. The stages may be summarized as follows:

Stage I: Clitoromegaly with no labial fusion
Stage II: Clitoromegaly with posterior labial fusion
Stage III: Pronounced clitoromegaly, single perineal urogenital orifice, and almost complete labial fusion
Stage IV: Increasingly penile clitoris, urethra-like urogenital sinus at base of clitoris, and complete labial fusion
Stage V: Penile clitoris, urethral meatus at the tip the of phallus, scrotum-like labia which is male in appearance, though without palpable gonads

4.04.5.1.2 Internal Genitalia

In contrast to development of the external genitalia, internal genital virilization is induced by interaction with anti-Müllerian hormone (AMH), which is produced by testicular Sertoli cells in males. AMH inhibits development of paramesonephric, or Müllerian, ducts that would otherwise develop as female reproductive structures (i.e., uterus, fallopian tubes, ovaries). Because a developing female fetus does not possess testes, or testicular products such as AMH, Müllerian structures do not regress as part of genital virilization. Therefore, internal genital development in girls with CAH should proceed as normal and with the possibility of normal fertility (New et al., 2013a).

4.04.5.1.3 SW 21OHD CAH

CAH owing to 21-hydroxylase deficiency may be divided into classical and NC forms. The classical form may be further divided into SW (~75% of cases) and SV forms (~25% of cases), depending on the degree of impairment in 21-hydroxylase enzyme function (Nimkarn et al., 2007a). Because the mineralocorticoid pathway, and aldosterone production, requires only minimal enzyme activity, SW occurs with more severe enzyme impairment (see Table 2). In both female and male infants, aldosterone deficiency may precipitate salt-losing crises with vomiting, weight loss, lethargy, dehydration, hyponatremia, and hyperkalemia. If untreated, such crises can lead to shock and even death. However, in females, androgen-related genital ambiguity typically leads to early diagnosis. Because physical appearance in boys is typical, except for potential subtle hyperpigmentation and penile enlargement, detection of the more severe form of the disorder may occur as late as 7–14 days of life with a salt-losing crisis. Earlier detection and avoidance of salt-losing crises depends on prenatal or newborn screening for the disorder.

4.04.5.1.4 SV 21OHD CAH

Patients with the SV form of 21OHD do not experience mineralocorticoid deficiency due to a greater degree of function of 21-hydroxylase. However, genital ambiguity in females is generally present at birth and will progress postnatally, if untreated. Such cases may show pseudoprecocious puberty, rapid somatic growth, and advance epiphyseal maturation likely leading to short stature.

4.04.5.1.5 Nonclassical 21OHD CAH

NC-21OHD, also called late-onset CAH, is more common than the classical form, with an incidence as high as 1:27 in certain ethnic minorities (Speiser et al., 1985). Due to milder enzyme deficiency, such cases generally present with signs of hyperandrogenism which develop postnatally, usually in early childhood. Females with NC-21OHD do not present with ambiguous genitalia at birth. As with cases of SV 21OHD, both males and females with NC-21OHD may continue to show signs of chronic androgen exposure if untreated. Symptoms can include early onset of facial, axillary, and pubic hair; adult body odor; and rapid somatic growth and bone age advancement. Where serum

Table 2 Clinical features of classical and nonclassical 21OHD CAH

Feature	*Classical 21OHD (salt-wasting)*	*Classical 21OHD (simple-virilizing)*	*Nonclassical 21OHD*
Prenatal virilization	Present in females	Present in females	Absent
Postnatal virilization	Present in males and females	Present in males and females	Variable
Salt-wasting	Present in males and females	Absent	Absent
Cortisol deficiency	Present in males and females	Present in males and females	Absent

cortisol concentration in classical 21OHD CAH is typically low, it is often normal in NC-21OHD.

Detection of NC-21OHD can be variable, depending on degree of enzyme deficiency and severity of symptoms. In childhood, precocious puberty and rapid growth may lead to clinical attention. However, symptoms may not be apparent until later in life. Women with NC-21OHD may present with variable and organ-specific effects of androgen excess, including hirsutism, temporal baldness, acne, and infertility. Menses may be delayed and secondary amenorrhea is common. Polycystic ovarian syndrome (PCOS) is also common as a secondary complication (Moran et al., 2000). One possible explanation for the presence of PCOS is chronic excess of adrenal androgens may disrupt gonadotropin release, directly affecting the ovary. Alternatively, early reprogramming of the HPA may influence its development. Because of symptom overlap with PCOS, NC-21OHD should be considered in women diagnosed with NC-21OHD (Azziz et al., 2006; Moran et al., 2000). In adult males, symptoms of androgen excess may include early balding, acne, short stature, or infertility (Cabrera et al., 2001; Urban et al., 1978).

4.04.5.2 Other Forms of CAH

11β-Hydroxylase deficiency is generally characterized by virilization and low-renin hypertension (Nimkarn and New, 2008). Despite aldosterone deficiency, excess production of deoxycorticosterone may cause salt retention and hypertension, though evidence of such effects is not usually apparent until late childhood or early adolescence. Furthermore, clinical signs of mineralocorticoid excess and degree of virilization are not linearly related. Hence, a strongly virilized female may be normotensive, whereas a mild virilization may be seen in conjunction with highly elevated blood pressure (Ferrari, 2002; Zachmann et al., 1983).

Clinical presentation of the classic form of 3β-hydroxysteroid dehydrogenase (3β-HSD, type II) deficiency is unique among CAH disorders. It is the only form of CAH in which both male and female infants may present with ambiguous genitalia. The type II 3β-HSD enzyme is expressed in the adrenal cortex and gonads and is responsible for the formation of progesterone, and ultimately for 17-OHP, cortisol, androstenedione, testosterone, and estrogen (Krone and Arlt, 2009). Hence, deficiency of 3β-HSD in the classic form results in insufficient testosterone and undervirilization in male infants. However, elevated levels of DHEA can produce moderate virilization in females as it is converted to testosterone in the liver. In the severe form, 3β-HSD deficiency may result in SW in both male and female infants (Pang, 2001).

17α-Hydroxylase/17,20-lyase deficiency affects steroid synthesis in both the adrenals and the gonads. Impaired cortisol synthesis leads to oversecretion of ACTH, deoxycorticosterone, and corticosterone resulting in low-renin hypertension, hypokalemia, and metabolic alkalosis. Female infants with this enzymatic deficiency are born with normal female anatomy; however, pubertal development is impaired as the ovaries do not produce sex steroids. Male infants present with varying degrees of undervirilization (New et al., 2013c).

Congenital lipoid adrenal hyperplasia is an exceptionally rare, yet severe, form of the disorder. It derives from errors in the earliest stages of steroid hormone synthesis: the transport of cholesterol into the mitochondria and the conversion of cholesterol to pregnenolone, which is the first step in the synthesis of all steroid hormones (Bose et al., 2000, 1996). Males with the most severe form of lipoid CAH are born with completely female-appearing genitalia. Genitalia in female newborns appear normal, but will remain infantile without treatment. There is SW in both males and females, which can be fatal if the disorder is undetected. In less severe forms, where there is partial protein function, salt loss may be more mild and genital ambiguity in males can be variable (Sahakitrungruang et al., 2010).

4.04.5.3 Postnatal Growth and Puberty in CAH

Table 3 shows patterns of growth, pubertal development, and fertility for the various subtypes of CAH. Continued exposure to excessive androgens in the postnatal period due to untreated 21OHD may cause progressive penile or clitoral enlargement and symptoms of precocious puberty, such as premature pubic and axillary hair and acne. Hyperandrogenism may also cause premature epiphyseal maturation and closure which, in

Table 3 Patterns of growth, pubertal development, and fertility for the various forms of CAH

	Females			*Males*		
CAH Subtype	*Growth*	*Puberty*	*Fertility*	*Growth*	*Puberty*	*Fertility*
21OHD CAH						
Classical salt-wasting	Short stature	Spontaneous/early[a]	Impaired	Short stature	Spontaneous/early[a]	Variable fertility[c]
Classical simple-virilizing	Short stature	Spontaneous/early[a]	Variable fertility[c]	Short stature	Spontaneous/early[a]	Variable fertility[c]
Nonclassical	Short stature	Precocious[b] potential amenorrhea	Variable fertility[c]	Short stature	Precocious[b]	Variable fertility[c]
11β-Hydroxylase CAH	Short stature	Normal	Normal	Short stature	Precocious[b]	Normal
3β-HSD CAH	Normal	Precocious[b]	Mostly infertile	Normal	Precocious[b]	Variable fertility[c]
17α-Hydroxylase CAH	Normal	Impaired	Variable fertility[c]	Normal	Impaired	Variable fertility[c]
Lipoid CAH	Normal	Impaired	Variable fertility[c]	Normal	Impaired	Mostly infertile

[a]Early refers to onset that is early within the normal age range.
[b]Precocious refers to early onset outside of the normal age range.
[c]Fertility rates depend to some extent on the degree of enzyme dysfunction.

conjunction with rapid linear growth, can result in final adult height that is below expectation based on parental heights. Historically, it has been believed that height outcomes would be unavoidably poor, with reported final adult heights of −2 standard deviations (SDs) or worse (Ghali et al., 1977; Urban et al., 1978). Meta-analysis has shown, however, that with early diagnosis and good treatment compliance, final adult height is often within 1 SD of an individual's target height.

Research looking at pubertal outcomes has suggested that, for most cases of 21OHD CAH treated from early life, the onset of puberty occurs at about the expected chronological age (Ghali et al., 1977; Jones and Verkauf, 1971). However, subsequent research has suggested that both boys and girls with 21OHD CAH may enter puberty slightly earlier than their unaffected peers. A study of male and female adolescents with classical and NC 21OHD found that males with the SV form of 21OHD CAH entered puberty the earliest of all groups (Nimkarn et al., 2007b). Following the onset of puberty, development of secondary sex characteristics appears to be normal. In cases involving 17α-hydroxylase/17,20-lyase deficiency, puberty will not be spontaneous due to deficient gonadal hormone production, and therefore must be artificially induced as part of overall clinical management (Miller et al., 1997). Similarly, in congenital lipoid adrenal hyperplasia, deficient gonadal hormone synthesis means that male sufferers will require clinically managed puberty. In contrast, by the age of puberty, females with congenital lipoid adrenal hyperplasia usually have enough estradiol to initiate breast development and possibly even menarche, although adrenal androgen is minimal and so development of pubic or other body hair is scarce (Bose et al., 1996; Sahakitrungruang et al., 2010).

4.04.5.4 Fertility in CAH

Females with 21OHD CAH may experience impaired fertility for a variety of reasons, including anovulation, secondary PCOS, irregular menses, nonsuppressible progesterone levels, or impact of anatomical abnormalities on coitus. Ovulatory failure secondary to ACTH oversecretion in early life is an important barrier to conception, though other factors may also contribute (Azziz and Slayden, 1996). These include (1) potential hyperresponsiveness to CRH; (2) altered enzyme kinetics, namely reduced catalytic efficiency of the mutated 21-hydroxylase with resulting increases in the precursor hormones progesterone and 17-OHP, even with glucocorticoid administration; (3) overactivation of the renin–angiotensin–aldosterone axis with ensuing stimulation of adrenocortical biosynthesis; and (4) alterations of the hypothalamic–pituitary–ovarian axis. In addition, research looking at psychological factors associated with 21OHD CAH in females has also suggested that masculinization of the fetal brain may also contribute to reduced heterosexual activity and/or reduced interest in becoming pregnant (Hines et al., 2004; Money and Schwartz, 1977). Because the degree of severity of the disorder will impact many of the factors listed above, females with the SV form of 21OHD CAH are more likely to become pregnant and to carry the pregnancy to term compared to those with the more severe SW form (Meyer-Bahlburg, 1999; Mulaikal et al., 1987). Females with other forms of CAH show varied rates of fertility, with impairment in 3β-hydroxysteroid dehydrogenase CAH, 17α-hydroxylase CAH, and lipoid CAH. Women with 11β-hydroxylase CAH show mild or no infertility (New, 2006).

In males with 21OHD CAH, reported fertility ranges from normal to severely impaired (Jääskeläinen et al., 2000; Urban et al., 1978). Development of testicular adrenal rest tumors (TARTs) is believed to be the primary factor affecting fertility rates (Falhammar et al., 2012), though chronic elevation of adrenal androgens due to under- or overtreatment with glucocorticoids may also suppress the hypothalamic–gonadal axis, resulting in small testes and decreased spermatogenesis (Cabrera et al., 2001). In addition, a study of 30 males with 21OHD CAH found that elevated fat mass was associated with pathological semen and subsequent infertility (Falhammar et al., 2012). As with females, males with other forms of CAH show varied rates of fertility. While those with lipoid CAH are nearly 100% infertile, those with 11β-hydroxylase CAH show little or no impairment, and cases of 17α-hydroxylase CAH or 3β-hydroxysteroid dehydrogenase CAH show impairment depending on the severity of the enzyme deficiency.

4.04.6 Diagnosis and Treatment

4.04.6.1 Diagnosis

A potential diagnosis of CAH should be considered in the case of obvious physical symptoms, such as ambiguous genitalia. Biochemical diagnosis of the most common form of CAH, 21OHD, can be confirmed by hormonal evaluation. Very high concentration of 17-OHP in a randomly timed blood sample can be diagnostic. A corticotropin stimulation test, measuring 17-OHP and Δ4-androstenedione at baseline and after 60 min, is the standard for establishing hormonal diagnosis of classical 21OHD CAH, and it is crucial for the diagnosis of NC-21OHD CAH, as 17-OHP values alone may not be sufficiently elevated to allow accurate diagnosis. However, it is important to note that this stimulation test should not be carried out during the initial 24 h of life as corticotropin levels tend to be elevated in the first 24 h for all newborns, and there is potential for a false-positive result. Noninvasive urine collection for assessment of steroid hormone metabolites and precursor/product ratio assessments can be measured in conjunction with serum steroid assays to increase accuracy and confidence in distinguishing the separate enzymatic forms of CAH (Shackleton, 1986). Genetic analysis may be carried out to confirm the specific genetic mutation, which may be useful for prognosis in classical 21OHD CAH given reported predictive phenotype–genotype relationships.

4.04.6.2 Prenatal Diagnosis

Due to the nature of transmission of CAH, parents who are known carriers may anticipate the possibility of having a child with CAH and may request prenatal diagnosis. The current standard of care for prenatal diagnosis of 21OHD CAH utilizes chorionic villus sampling (CVS) or amniocentesis for molecular genotyping of *CYP21A2*, for which ~95% of mutations have been identified (Ohlsson and Schwartz, 1996; Tukel et al., 2003). CVS is usually performed between weeks 9 and 11 of gestation, while amniocentesis is undertaken in the second trimester. The timing of a prenatal diagnosis is of particular

importance when considering prenatal treatment with dexamethasone to prevent genital virilization in a female fetus.

The risk of having an affected fetus is one in four, and since half of those will be male, only one fetus in eight will be a female at risk for genital virilization. Because genital organogenesis begins around week 7 of gestation, prenatal treatment must be initiated before a diagnosis is confirmed by CVS or amniocentesis, resulting in unnecessary treatment in seven out of eight at-risk pregnancies. Although some studies have reported no adverse long-term sequelae in mothers or offspring treated unnecessarily with dexamethasone (Meyer-Bahlburg et al., 2012; New et al., 2012), others have suggested cognitive impairment (Hirvikoski et al., 2007).

In 1997, the presence of fetal DNA in maternal plasma and serum was discovered (Lo et al., 1997), allowing for the first time for noninvasive prenatal diagnosis. By extracting fetal DNA from maternal blood at 6–7 weeks of gestation, the presence of the sex-determining region of the Y chromosome (SRY) can be used to determine the genetic sex of the fetus. In the absence of SRY, indicating a female fetus, DNA analysis may be carried out. This noninvasive technique offers the advantage of earlier detection of CAH, and avoidance of unnecessary treatment with dexamethasone in males or unaffected females, and eliminates the risk of spontaneous miscarriage associated with invasive procedures such as CVS or amniocentesis. Furthermore, a study of the efficacy of this approach reported that sex and CAH status were correctly deduced with 100% accuracy (New et al., 2014).

4.04.6.3 Hormone Replacement

The aims of hormone therapy in CAH are to correct the deficiency in cortisol and to suppress overproduction of ACTH. Glucocorticoid replacement reduces production of precursors in the androgen pathway, therefore preventing further virilization. Treatment of classical 21OHD CAH usually entails about 10–15 mg/m^2 per day hydrocortisone divided into two or three doses. Higher levels of enzyme function in NC-21OHD CAH result in lower doses of hormone replacement. Further antiandrogen treatment may be advised for adult women with continued hyperandrogenization despite adequate adrenal suppression. In all cases, the goal of corticosteroid treatment is to administer the lowest dose possible for optimal biochemical control. Optimization may be assessed by measuring 17-OHP and androstenedione. Serum testosterone may also be measured in females and prepubertal males. Dosing should be aimed at age- and sex-appropriate androgen levels. Overtreatment, 17-OHP >1000 ng dl^{-1}, should be avoided as it may lead to Cushing syndrome (New et al., 2013c).

Individuals with SW 21OHD CAH must also be treated for elevated plasma renin. The standard dose is 0.1 mg daily (range 0.05–0.2 mg) of 9α-fludrocortisone acetate. Infants are often also treated with salt supplements, such as sodium chloride (1–2 g daily), with the necessity of fludrocortisone treatment appearing to diminish with age. As with corticosteroid treatment, the goal with fludrocortisone treatment is to give the lowest dose necessary to resolve the sodium deficient state without oversuppression of plasma renin activity. Efficacy of mineralocorticoid therapy may be monitored using plasma renin and aldosterone measurements (New et al., 2013c).

The goals for treatment for 11β-OHD are to provide cortisol replacement, to minimize sex steroid hormone excess and subsequent virilization (in females), and to normalize blood pressure. Administration of 10–15 mg/m^2 per day hydrocortisone divided into two or three doses across the day is similar to treatment of 21OHD CAH. In both 3β-HSD CAH and lipoid CAH, glucocorticoid and mineralocorticoid treatment are standard. Patients with 17α-hydroxylase/17,20-lyase deficiency are typically treated for excess DOC and low-renin hypertension. Glucocorticoid replacement is usually sufficient to normalize both. In some cases, such as 3β-HSD CAH, 17α-hydroxylase/17,20-lyase deficiency, and lipoid CAH, sex steroid replacement should be added to the treatment regime in a sex- and age-appropriate manner to allow for sexual development consistent with the peer group.

During episodes of increased physiologic stress, glucocorticoid dosing may be increased to provide adequate coverage. Emergency injection kits are usually given to families to cover episodes of non-life-threatening illness, with recommended increases of up to three times the normal daily dose. In cases of surgery, up to 10 times the daily dose of glucocorticoid replacement may be required in the first 48 h following the procedure. Further supplementary treatments have been implemented, for example, to increase final adult height. Because excess sex steroid production in CAH may accelerate growth velocity, ending up with premature epiphyseal maturation and closure, growth hormone in conjunction with a GnRH analog may be administered (Klingensmith et al., 1977; Nimkarn and New, 2007).

4.04.6.4 Surgery

Historically, it has been routine to recommend surgery to correct ambiguous genitalia associated with some forms of CAH in female-assigned infants. However, due to concerns about long-term outcome, such interventions have become increasingly fewer. Limited studies have suggested reduced sensitivity and impaired sexual functioning in female patients who have had genitoplasty (Crouch et al., 2008; Nordenstrom et al., 2010). Furthermore, those with the more severe form of the disorder are reported to have had a greater number of surgeries and poorer outcomes. However, surgical techniques and mapping of female genital innervation and anatomy have improved dramatically in the last 50 years, making comparisons across cohorts difficult to interpret. Older women included in such research may have had clitorectomy, for example, which is no longer performed under any circumstance. The recent trend, in fact, has been away from any surgical intervention until the patient herself can give informed consent to any procedure, though medical indication for early surgery may be given in cases of recurrent urinary tract infections due to pooling of urine in the urogenital sinus.

Though data are scarce, studies are now reporting comparisons of sexual functioning in women who have undergone surgical correction to that in women for whom such interventions were not necessary or deferred (Callens et al., 2012; van der Zwan et al., 2013). Critically, the most comprehensive study has shown that risk for sexual dysfunction was high for women with genital abnormalities, whether or not they had surgical intervention (Callens et al., 2012). This suggests that attention to difficulties associated with

genital malformations should not be shunted into a debate regarding surgical intervention, but rather given toward provision of psychosocial and psychosexual support in recognition of inherent challenges.

4.04.6.5 Bone Mineral Density

Because glucocorticoid replacement aimed at suppressing excessive adrenal steroids in CAH may not always accomplish normal biological variations in serum cortisol, the necessary dosage may at times be supraphysiological. Such glucocorticoid excesses have been shown to lead to abnormalities of bone mineral density (BMD), in endogenous Cushing syndrome, for example, by increasing bone reabsorption and decreasing bone formation. However, reports of BMD in CAH have produced conflicting results with some suggesting increases in BMD, while others suggest decreases or normal bone maturation (Arisaka et al., 2001; Fleischman et al., 2007; Girgis and Winter 1997; Zimmermann et al., 2009). Though mechanisms are not well understood, a recent study of subgroups of CAH found that patients with classical 21OHD CAH had lower BMD compared to patients with NC-21OHD CAH and suggested a possible link between disease-related DHEAS deficiency and weak cortical bone independent of glucocorticoid exposure (El-Maouche et al., 2015).

4.04.7 Androgens, Brain, and Behavior

Androgenic influences on neurobehavioral development were first demonstrated in a landmark study by Phoenix et al. (1959). Administration of testosterone to pregnant guinea pigs resulted in female offspring who displayed increased capacity for male-typical sexual behavior, and decreased capacity for female-typical sexual behavior, in adulthood. The authors formulated the hypothesis that exposure to testosterone during critical periods of neural development influences the *organization* of brain structures and systems with a degree of permanence; and they contrasted such effects with later, *activational*, effects that induced transient changes in the previously organized brain systems (Phoenix et al., 1959). Subsequent research has supported the organizational/activational distinction and has extended the original findings to include wider ranges of affected sexually dimorphic behaviors and animal species (Hines, 2004, 2009). For example, female rhesus macaques exposed to testosterone during fetal development showed increases in male-typical sexual and nonsexual behaviors in adolescence and adulthood, such as mounting and rough-and-tumble play (Alexander and Hines, 2002).

Though caution is warranted when generalizing findings from the animal literature to human development, extensive research with nonhuman mammals has established three basic principles that apply across species (Hines, 2011): (1) Fetal development in the absence of testosterone will be female-typical, i.e., estrogens do not promote female-typical development; (2) The masculinizing effects of testosterone are exerted in a graded and linear fashion, i.e., greater exposure to testosterone results in greater masculinization of brain structures and behavior; (3) Neurobehavioral sexual differentiation is multidimensional, i.e., behaviors and brain structures that differ between sexes may not interrelate in a uniform manner, resulting in complex patterns of sex-typed behavior. Generally speaking, however, human behaviors that have been shown to reliably differ between males and females may be conceptualized within four broad domains, including gender role behavior, gender identity, sexual orientation, and cognitive functioning. Development within these domains has been widely studied in girls, and to a lesser extent in boys, with classical 21OHD CAH, given their potential for having had increased exposure to testosterone during fetal development.

4.04.7.1 Gender Role Behavior in 21OHD

Sex differences in human behavior are largest during childhood and may be reliably observed in preferences for toys and activities, playmates, play styles (Hines, 2011). Compared to girls, boys tend to play more with toys such as vehicles and weapons, they tend to prefer boys as playmates, and they engage in more rough-and-tumble and aggressive play; By contrast, and compared to boys, girls tend to play more with dolls and tea sets, they tend to prefer girls as playmates, and they engage in less rough-and-tumble and aggressive play (Hines, 2004).

Studies of children with 21OHD CAH have reliably found that the girls with the condition show increased masculine, and decreased feminine, gender role behavior (Berenbaum and Hines, 1992; Dittmann et al., 1990; Ehrhardt and Meyer-Bahlburg, 1981; Hines, 2004). For example, compared to unaffected sisters, girls with 21OHD CAH tend to play more with boys' toys (Pasterski et al., 2005) and less with girls' toys, they more often prefer boys as playmates (Pasterski et al., 2011), and they engage in more rough-and-tumble and aggressive play (Pasterski et al., 2007). Furthermore, it seems that the masculinization of these sex-typed behaviors depends to some extent on the degree of prenatal testosterone exposure, which may be ascertained by degree of genital virilization and gene mutation analysis (Nordenstrom et al., 2002). Boys with CAH do not generally show alterations in childhood gender role behavior.

Some have suggested behavior in girls with CAH may be more masculine due to socialization by parents. That is, parents of the girls with CAH may socialize their daughters more like boys in response to their virilized appearance at birth (Quadagno et al., 1977; Wong et al., 2013). However, an observational data suggest that parents give equal or greater encouragement of female-typical play in their daughters with 21OHD CAH compared that given to their unaffected daughters (Pasterski et al., 2005). In addition, there appears to be an inverse relationship between parental encouragement of, and actual play with, girls' toys. In the study by Pasterski et al. (2005), the more encouragement the girls with 21OHD CAH received, the less likely they were to engage in the desired behavior. Alternatively, it could have been that parents of strongly masculinized daughters felt more compelled to encourage female-typical behavior.

Effects of socialization more generally have also been studied in girls with 21OHD CAH (Hines et al., 2016). In this case, the researchers looked at children's responses to modeling and labeling of sex-appropriate behavior by adults other than parents. Whether demonstrated by models or explicitly labeled, children generally express preferences for objects

that have been deemed appropriate for their gender. However, girls with 21OHD CAH showed reduced responses to information about sex-appropriate behavior (Hines et al., 2016). This suggests that neural exposure to androgens beginning prenatally may influence gender-related behavior directly as well as by altering mechanisms responsible for socialization of gendered behavior.

4.04.7.2 Gender Identity and Sexual Orientation in 21OHD

Gender identity refers to the fundamental sense of self as male, female, or, in rare cases, neither/both (nonbinary). In the general population, there is a very large sex difference in gender identity; that is, the vast majority of genetic/phenotypic males identify as male and the vast majority of genetic/phenotypic females identify as female. The prevalence of a cross-gender identity is low, with rates estimated to be about 0.005–0.014% in adult natal males and 0.002–0.003% in adult natal females (APA, 2013). Likewise, sexual orientation in adulthood shows a very large sex difference with the majority of natal females reporting sexual attractions toward males and the majority of natal males reporting sexual attractions toward females (Diamond, 2008; Rahman et al., 2012). Perhaps not surprisingly, studies of women with 21OHD CAH have suggested decreases in heterosexual orientation (Hines et al., 2004) and that the degree of nonheterosexual interest/behavior may be correlated with degree of prenatal testosterone exposure (Meyer-Bahlburg et al., 2008).

In contrast to consistent findings in studies of gender role behavior and sexual orientation in females with CAH, results from studies of gender identity have been less consistent. A review of the literature (Pasterski et al., 2015) found that while ~60% of studies reported a shift toward cross-gender identification in females with 21OHD CAH, 40% suggested no such changes. However, the same report also presented new data on gender identity in a cohort of 4- to 11-year-old girls, in a large sample and using standardized assessment that had been lacking in some previous studies. They reported that 12.8% of the sample met the clinical criteria for gender dysphoria (GD) (Pasterski et al., 2015), which is decidedly more frequent than found in the general population. Note, however, that a diagnosis of GD requires that a child state the wish to have the physical characteristics of the other sex and that he/she is distressed by his/her own physical sexual characteristics, i.e., their genitalia. This criterion is difficult to apply in cases where a child has ambiguous or surgically corrected genitalia. Furthermore, there was no evidence in this study that the girls with CAH experienced significant distress related to their cross-gender ideation. Nevertheless, the preponderance of data suggests an increased risk for cross-gender identification in girls with CAH.

Higher than expected rates of gender change in cases of both male- and female-assigned 46,XX CAH suggest that implications of alterations in gender identity are highly complex. Although many fewer 46,XX CAH are assigned male, compared to that assigned female, data from such cases have been cited as support for routine consideration of male assignment in the most strongly virilized cases (Lee and Houk, 2010). Advocates suggest that, given the relatively linear relationship between androgen exposure and neurobehavioral masculinization, a male gender assignment may be more in line with the often observed masculine gender role and sexual orientation. Furthermore, a male assignment would reduce the need for corrective genital surgeries. However, others have suggested that preservation of (potential) fertility, evidence of regular acceptance of the female gender assignment, and movement away from cosmetic surgical interventions for virilized genitalia argue for female assignment in all cases (Dessens et al., 2005).

4.04.7.3 Cognition in 21OHD

Generally speaking, there is no reason to expect compromises in cognitive functioning in individuals with CAH. Studies looking at general intelligence have found no differences between children with and without CAH (Collaer et al., 2016; Malouf et al., 2006). Furthermore, sex differences in cognitive abilities that may be attributed to androgen exposure are, on average, small. However, given historical findings that males have outperformed females in mathematics and certain visuospatial tasks, research in these domains has looked closely at performance in individuals with CAH, primarily to ascertain potential effects of prenatal testosterone on reported sex differences. Taken together, however, the bulk of studies have produced mixed results. For example, when considering the visuospatial task that shows the largest sex difference, the mental rotations task, three studies reported enhanced performance in females with CAH (Berenbaum et al., 2012; Hampson and Rovet, 2015; Resnick et al., 1986), while four studies found no effects (Baker and Ehrhardt, 1974; Helleday et al., 1993; Hines et al., 2003; Malouf et al., 2006). Similarly, in studies of boys with CAH, results have suggested either no effects (Baker and Ehrhardt, 1974; Resnick et al., 1986) or diminished visuospatial abilities (Berenbaum et al., 2012; Hines et al., 2003).

Results from studies of mathematics ability in children with CAH have led researchers to investigate potentially detrimental cognitive effects associated with treatment of the condition, rather than those associated with the condition itself. Starting with the hypothesis that prenatal exposure to excess androgens may enhance certain abilities that have shown a sex difference favoring males, researchers instead have found that children with CAH showed reduced quantitative performance (Baker and Ehrhardt, 1974; Perlman, 1973; Sinforiani et al., 1994). Further investigation has revealed impairment in short-term memory in both males and females with 21OHD CAH in childhood, adolescence, and adulthood (Browne et al., 2015; Collaer et al., 2016). Although disease-related factors such as hyponatremia or SW crises cannot be ruled out as contributing factors, chronic elevations of glucocorticoids administered to treat hormone deficiencies seem the most likely contributor to reductions in short-term memory (Collaer et al., 2016). This conclusion is supported by research with nonhuman mammals showing hippocampal atrophy and memory impairments subsequent to glucocorticoid manipulations (Herbert et al., 2006; McEwen and Sapolsky, 1995). Increased monitoring of glucocorticoid treatments, along with educational interventions, may be employed to negate potential iatrogenic effects of glucocorticoid treatment on cognition in individuals with CAH.

Recent lines of inquiry investigating mechanisms underlying autism spectrum conditions (ASC) have led to studies

including children with CAH. A high preponderance of males diagnosed with ASC suggests a possible role for neurobehavioral effects of prenatal testosterone exposure. Although some evidence has been reported to support the fetal testosterone theory of autism (Baron-Cohen, 2004), these findings have not been independently corroborated. On the contrary, convergent evidence, including studies of children with CAH and typically developing children, suggests no relationship between increased exposure to prenatal testosterone and autistic traits (Kung et al., 2016). There is currently no evidence of elevated risk for autism in children with CAH.

4.04.8 Clinical Challenges

4.04.8.1 Prenatal Therapy and Outcome

Prenatal treatment for 21OHD using dexamethasone was first implemented in 1978 (David and Forest, 1984) and has been employed in the United States since 1986 (New et al., 2001). Initiation of therapy before the onset of adrenal androgen secretion, between weeks 7–9 of gestation, is effective for suppressing excessive androgen production and prevents genital virilization in affected female fetuses. Although maternal side effects have been reported and should be monitored throughout pregnancy (New et al., 2001), studies suggest that treatment with dexamethasone is generally well tolerated. In a study of 38 mothers treated with dexamethasone during pregnancy, all indicated that they would elect to undertake the treatment again should the circumstance arise (Trautman et al., 1996).

The potential for harmful neurological effects in developing fetuses treated unnecessarily (only one in eight will require continued treatment) has raised a great deal of concern, leading in some cases to cessation of the treatment altogether. Studies of unaffected children treated short term with dexamethasone have suggested impairment in working verbal memory and reduced self-perception of scholastic competence, compared to controls (Hirvikoski et al., 2007). However, other studies found no evidence of negative sequelae that could be linked to the dexamethasone treatment (Hirvikoski et al., 2008; Meyer-Bahlburg et al., 2012).

Advances in noninvasive prenatal sex determination and diagnosis of CAH using cell-free fetal DNA (cffDNA) have reduced the likelihood of unnecessary treatment in unaffected children (New et al., 2014). Because previous diagnostic techniques, such as amniocentesis and CVS, can only be applied after adrenal androgen secretion has begun in an affected fetus, all potential CAH pregnancies were treated until the CAH status of the fetus could be determined. This means that seven out eight fetuses would have been exposed unnecessarily to dexamethasone for several weeks. However, because cffDNA allows for sex determination and potential identification of mutations in the CYP21A2 gene responsible for 21OHD CAH as early as 5–6 weeks of gestation, instances of unnecessary treatment may be substantially reduced (New et al., 2014). Although some still consider prenatal administration of dexamethasone to be unnecessarily risky, no adverse outcomes have been clearly or consistently linked to the treatment. Benefits for CAH-affected females include avoidance of genital virilization and potential necessity for corrective surgeries. In cases of ambiguous genitalia in which corrective surgery is deferred, the potential for negative effects on psychosexual development remains a possibility. Because outcome data are sparse, however, it has been recommended that no further prospective recruitment for prenatal treatment should be made until large-scale retrospective analysis of development in existing cases of dexamethasone exposed unaffected individuals has been established.

4.04.8.2 Transition to Adult Services

Because most cases of CAH will require lifelong clinical management, challenges unique to each life stage must be considered. Management in a multidisciplinary clinic with close communication between specialists in pediatrics and adult medicine is optimal (Houk et al., 2006; Hughes, 2004b). Input across the life span may include subspecialists in endocrinology, urology, gynecology, reproductive medicine, and psychology. **Table 4** highlights the challenges and considerations relevant in infancy and childhood to adolescence and adulthood. Monitoring growth and treatment efficacy and compliance in young children is important. In adolescence, the goals of treatment shift toward preventing hyperandrogenism in females, preserving fertility, and establishing satisfactory sexual functioning. Furthermore, specialist input relevant to psychosexual development may be warranted, particularly in cases of genital ambiguities or corrective surgeries. In adulthood, the potential development of PCOS should be considered in female patients, while male patients may be at risk for testicular adrenal rest tumors (Hughes, 2004b).

Handover from pediatrics to adult services may prove challenging. A study investigating the transition in a single center over 18 found that up to 50% of their patients were lost to follow-up once they were discharged from pediatrics (Gleeson et al., 2013). Only 53% of patients identified for the

Table 4 Age-related considerations for clinical management of congenital adrenal hyperplasia (CAH) across the life span

Infancy	*Childhood/Adolescence*	*Adulthood*
Accurate diagnosis	Growth velocity	Hyperandrogenism in females
Establish treatment regime	Medication compliance	Secondary PCOS in females
Monitor salt loss (if necessary)	Induction/management of puberty	Adrenal rest tumors in males
Surgical intervention (if necessary)	Psychosexual development in females	Fertility in both females and males
	Hyperandrogenism in females	Potential loss to follow-up
	Fertility in females and males	

investigation had attended the first two appointments within the adult services. However, those who were good early attenders were less likely to be lost to follow-up, suggesting that increased engagement with patients in this time of transition may have implications for long-term outcomes.

4.04.8.3 Treatment-Related Complications in 21OHD CAH

The complexities of managing CAH across the life span is perhaps most evident when considering the accumulation of disease- and treatment-related effects on life expectancy. Historically, some number of undiagnosed newborns would have perished due to misunderstood SW crises; however, scientific advancement and advent of screening has improved initial survival rates dramatically. With improved diagnostics, clinical management, and quality of life (QoL) in infancy and childhood, some studies have turned to characterizing CAH across the life span, with a focus on later adulthood CAH- and treatment-related complications. One result has been highlighted increases in adulthood cardiometabolic morbidities. For example, one study showed that patients with CAH were more likely to be obese compared to conspecifics in the UK population, and these patients presented with increased rates of metabolic abnormalities, such as hypercholesterolemia, and insulin resistance (Arlt et al., 2010). Another study found that cardiometabolic morbidities, including thyrotoxicosis, venous thromboembolism, atrial fibrillation, obesity, and diabetes, were nearly four times more likely in patients with CAH compared to the general population in Sweden, where the study was conducted (Falhammar et al., 2014).

Consideration of possible mechanisms for observed cardiometabolic morbidity has led some researchers to consider outcomes, such as insulin resistance or cardiovascular disease, in younger patients and as a function of treatment history. In a study of 37 children with classical and NC 21OHD CAH, those with the earlier onset classical form of the disorder showed increased fat mass, while those with the late-presenting NC form showed greater lean mass and increased parameters of insulin resistance (Williams et al., 2010). This suggests that while long-term glucocorticoid therapy may have caused increased fat mass, extended exposure to postnatal androgen may be responsible for increased insulin resistance. Another study of patients with CAH aged 20 years and younger revealed significantly increased early signs of atherosclerosis. This finding, however, was independent of obesity status and only present in females (Rodrigues et al., 2015), suggesting further possible treatment-related causal factors, especially when considered in light of another finding linking glucocorticoid dose to blood pressure (Han et al., 2013). This study, of 196 adults with CAH, found that patients with the more severe form of the disease received higher glucocorticoid doses that were also associated with hypertension. The difficulty is in balancing potential ill-effects of poor control, i.e., hyperandrogenism, with iatrogenic effects of overtreatment, i.e., hypercortisolism.

To add to the challenge, there appears to be a great deal of variance in pharmacokinetics of hydrocortisone across age stages and between individuals, making it clear that close monitoring and highly individualized treatments would be optimal. With the goal of mimicking of physiological hormone production, which would reduce instances of overtreatment during episodes of increased physiologic stress, clinical researchers are testing new options. For example, pump delivery of hydrocortisone could avoid gaps in between doses and may accommodate increased need via controlled infusion rate (Hindmarsh, 2014). Alternatively, oral treatments that more closely mimic physiological hormone production are in development. In either case, reducing treatment doses while adequately suppressing hormone overproduction is likely to reduce morbidities in adult life.

4.04.8.4 QoL Outcomes in 21OHD CAH

Psychosocial and QoL outcomes for individuals with CAH may be defined in a variety of ways. Some outcome studies have looked at general and practical factors including level of educational attainment, employment, marriage, and parental status (Falhammar et al., 2012; Strandqvist et al., 2014). Others have looked at self-perceived QoL, general psychological adaption, sexual satisfaction, and fertility (Berenbaum et al., 2004; Gastaud et al., 2007; Malouf et al., 2010; Wisniewski et al., 2004). Furthermore, parameters for assessing outcomes differ across the life span. For example, factors influencing QoL in childhood relate primarily to tracking developmental trajectories, while those in adulthood tend to be centered around romantic relationships and psychological health. Although results from studies of the various outcome factors have yielded conflicting results, possibly due to methodological variance, several narratives have consistently emerged.

In childhood, development of gender-related behavior may be atypical for girls exposed prenatally to higher levels of testosterone (Hines, 2004; Pasterski et al., 2007, 2005), and there appears to be a robust genotype–phenotype correlation for the developmental trajectory (Krone et al., 2013; Nordenstrom et al., 2002). However, the self-perception of the effects of atypical development on friendships and general well-being seems not to correlate in the same way. This suggests that there may be protective factors, such as coping mechanisms, that may shield sufferers from potentially negative outcomes (Nordenstrom et al., 2010). Studies of health-related QoL have consistently shown negative effects of having a lifelong illness, such as constant necessity for medication, and of condition-related physical characteristics, such as short stature and weight gain (Speiser and White, 2003).

In adulthood, self-perceived health-related QoL has been consistently reported as negatively affected, particularly in women (Arlt et al., 2010; Johannsen et al., 2006; Nermoen et al., 2010). Fertility has also been shown to be impaired, in both men and women (Falhammar et al., 2012; Gastaud et al., 2007); however, this appears to be partially driven by reduced coupling and/or interest in infants in women. Pregnancy rates have been reported as normal for those who seek fertility-related medical assistance (Casteras et al., 2009; Hagenfeldt et al., 2008).

QoL may also be ascertained by collecting data on objective factors considered requisite for positive outcome. An exceptionally large epidemiological study has quantified such factors for 90% of the 21OHD CAH population in Sweden (Strandqvist et al., 2014). Furthermore, they were able to classify all individuals according to type of CAH, i.e., SW, SV,

or NC, and they obtained molecular genetics information for more than 80%. This allowed them to look at potential unique relationships with differing outcomes. Outcome parameters included having a partner, being able to work and support oneself, staying healthy and independent, and for some, the possibility of having children.

In general, the study found that CAH patients did not differ from the general population. However, analyses revealed an increased risk of not completing primary education in females with SW and SV forms of 21OHD CAH. The risk was not increased for males. Candidate explanations included effects of glucocorticoid treatment and/or sequelae of hypoglycemia and/or salt-wasting crises on cognitive function. However, given that males would have been at greater risk for the latter episodes, this is an unlikely explanation. It is possible that higher doses of hydrocortisone were given to girls to prevent physical effects of excess androgens. Additional psychological and social problems associated with androgen excess that girls may encounter during early education may have affected relationships with peers and stress levels. Surprisingly, women in the SW group were no different from others in terms of employment, and they had an increased likelihood of being in the top 20th percentile income group, even though they were less likely to finish their education. This may be related to choosing jobs that are more often occupied by males and pay higher wages. Perhaps most importantly, this highlights the fact that CAH-related challenges and outcomes are different for males and females and effects may be more or less pronounced in different stages of life (Strandqvist et al., 2014).

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