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Non-Classic Congenital Adrenal Hyperplasia: What Do Endocrinologists Need to Know?

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1. Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic defects in cortisol synthesis. The altered negative feedback of cortisol to the hypothalamus and the pituitary gland prompts corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) elevations. Increased ACTH, in turn, has two downstream effects: 1) it overstimulates adrenal steroidogenesis, resulting in an accumulation of steroids above the enzymatic blockage; and 2) when sustained, ACTH elevation promotes adrenal gland enlargement (hence, the term CAH). A variety of mutations in one or more genes encoding enzymes essential for cortisol synthesis (Figure 1) lead to a spectrum of disorders and disease severity. In general, complete or nearly complete enzymatic defects result in overt adrenal insufficiency, and are conventionally referred to as “classic” CAH. In milder forms of the disease, also termed “late-onset” or “non-classic” CAH (NCCAH), partial enzymatic defects are overcome by ACTH elevations. These patients have compensated cortisol and aldosterone production. Defects in the gene encoding 21-hydroxylase (*CYP21A2*) account for more than 95% of all cases of CAH[1] and, unless otherwise specified, the term CAH will refer to 21-hydroxylase deficiency (21OHD) throughout this article. A brief overview of rare forms of CAH is presented in Table 1.

Patients with classic CAH are typically diagnosed at birth or early in life, and their transition of care to adult endocrinology occurs with the diagnosis previoulsly established. Conversely,

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adult endocrinologists must know when to suspect NCCAH, which has a considerably higher prevalence. In this review, we will focus primarily on NCCAH.

2. Epidemiology

The worldwide incidence of classic CAH is roughly 1:14,000 to 1:18,000 births[2]. In contrast, NCCAH, is relatively common, with an overall prevalence of 1:200 in the Caucasian US population,[2,3] and a higher frequency among Ashkenazi Jews, Hispanics, Mediteraneans, Middle Eastearns, and Eskimos[4]. Among women presenting with symptoms of androgen excess, the overall prevalence of NCCAH is approximately 4%[5].

3. Genetics of CAH

The *CYP21A2* gene is located on the long arm of chromosome 6, within the human leukocyte antigen (HLA) locus and adjacent to the genes for the fourth component of complement[6–8], a region within which genetic recombinations occur frequently[9]. A highly homologous non-functional pseudogene *(CYP21A1P)*, which encodes a truncated, inactive enzyme, also resides in the vicinity[10]. Most patients with NCCAH are compound heterozygotes with different mutations in the two alleles[5]. Mutations that fully annul 21-hydroxylase activity, such as complete deletions, large gene conversions, and non-sense or frame-shift mutations, lead to salt-wasting CAH, in which both glucocorticoid and mineralocorticoid production is lacking. Mutations that render even minimum residual enzyme activity lead to the so-called “simple virilizing” CAH, where sufficient aldosterone synthesis occurs. In NNCAH, 20–60% of the enzyme activity is preserved, which ensures cortisol concentrations equal to those of unaffected individuals. NCCAH patients might harbor one classic and one non-classic allele or two non-classic alleles. Parents with NCCAH have a 1.5–2.5% risk of having a child with classic 21OHD[11,12]. Thus, *CYP21A2* genotyping in patients with 21OHD and their partners can refine the risk of having an affected offspring[2].

Although a strong genotype-phenotype correlation exists for the most severe and the mildest forms of CAH, the clinical manifestations of moderate CAH forms are quite variable[13,14]. Certain mutations, such as P30L, I172N or I2G, and combinations of mutations (homozygous vs. heterozygous) can yield different phenotypes[14]. Characterizing the predominant phenotype for a given genotype can assist in genetic counseling of parents at risk of having a child with CAH.

4. Clinical features of patients with CAH

The clinical manifestations of CAH can result from cortisol and/or aldosterone deficiency when present (in classic CAH), and from excessive synthesis of bioactive steroids, which is prompted by ACTH and facilitated by the enzymatic blockade. In the case of 21OHD, variable degrees of androgen excess occur (Figure 1). In patients with classic 21OHD, in-utero exposure to profound androgen excess leads to virilization of the genitalia in girls, which is easily identified at birth. In contrast, affected boys have minimal or no physical findings, putting them at risk for incorrect or missed diagnosis when newborn screening is

not pursued. The implementation of newborn screening across all USA and several other countries has significantly decreased the death rates among infants with salt wasting 21OHD[2] and debunked the preponderance of disease in females.

Patients with NCCAH may present during childhood with premature pubarche, which has been described as early as 6 months of age[5]. In contrast, females with NCCAH often present as adolescents or young adults with acne, hirsutism, menstrual abnormalities, or infertility, features that overlap greatly with those of PCOS. Males with NCCAH often remain undiagnosed, or only identified during genetic screening performed for pre-conception counselling or after the birth of an affected offspring[5].

Female patients with non-classic 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) or 11β-hydroxylase (CYP11B1) deficiency (11OHD) present with similar clinical features with those with 21OHD and PCOS, but both are extremely rare forms of CAH[15,16]. The distinction between these types of non-classic CAH and PCOS is unreliable based on clinical presentation alone[17]. Hirsutism (59% in NCCAH and 60–70% in PCOS) and acne (33% in NCCAH and 14–25% in PCOS) occur at comparable rates in both disorders[18]. In constrast, menstrual irregularity (10–17% in women with NCCAH *vs* 75–90% in PCOS)[18,19] and infertility (approximately 13% in NCCAH *vs* 25–50% with PCOS) tend to occur more frequently among women with PCOS[18]. Similarly, polycystic ovarian morphology, although more common in PCOS, has also been reported in 30–40% patients with NCCAH[18,19]. Metabolic features typically associated with PCOS, including obesity, insulin resistance, and dyslipidemia, have also been reported in up to 40% of patients with NCCAH[18,19]. Although the prevalence of PCOS is about 40–50 times higher than that of non-classic 21OHD among women with hyperandrogenemia[18], testing for non-classic 21OHD should be pursued in all such patients, as the correct diagnosis has implications for treatment and family planning.

5. Biochemistry of CAH - implication for diagnosis and disease monitoring

5.1. Diagnosis of CAH

All enzymatic defects within the steroidogenic pathway generate a large precursor to product ratio (Figure 1), which is further enhanced by ACTH stimulation. The prominent elevation of the main substrate for the defective enzyme forms the basis of CAH diagnosis. For 21OHD, the diagnosis relies on17-hydroxyprogesterone (17OHP) elevations, which span a gradient reflective of the spectrum of enzymatic defects. Both neonatal and clinically-prompted screening for 21OHD consists in 17OHP measurement, and values >200 ng/dL (6 nmol/L) are suggestive of the diagnosis. Patients with classic 21OHD typically have 17OHP concentrations above 10,000 ng/dL. In patients with modest 17OHP baseline elevations, of 200–1000 ng/dL (6–30 nmol/ L), a cosyntropin stimulation test is the current standard-of-care, and 17OHP values >1000 ng/dL establish the diagnosis[2]. Because 17OHP follows closely the circadian rhythm of ACTH, blood should be obtained in early morning. After puberty, 17OHP should be measured during the follicular phase to detect NCCAH, as ovarian surges of 17OHP occur during the luteal phase of the menstrual cycle.

A caveat to CAH testing is that these diagnostic thresholds should be considered in the context of the assay methodology, population, and individual background. Some patients with NCCAH could be missed based on a 17OHP cutoff >200 ng/dL (> 6nmol/L),[20] and lower thresholds have been proposed, particularly when using mass spectrometry assays[17,20,21]. False positive 17OHP screening results are even more common, particularly when immunoassays are used, and when the blood sample is obtained in the luteal phase. Modestly elevated 17OHP is reported in 25% women with PCOS[19,22], likely because the high rates of irregular menses and amenorrhea make follicular phase testing impractical. Other tests suggestive of PCOS, such as elevated LH/ FSH ratio, have poor sensitivity and specificity and can also be seen in approximately 10% women with NCCAH[19]. Simultaneous elevation of 21-deoxycortisol, and lower corticosterone, further support the diagnosis of CAH[17,23]. Such multistoried panels could circumvent the need for cosyntropin-stimulated testing in the future.

17OHP is typically elevated in patients with classic HSD3B2 deficiency or 11OHD[1], although normal levels may be seen in non-classic forms[16]. The diagnosis of non-classic HSD3B2 deficiency is made when 17-hydroxypregnenolone exceeds 3,000 ng/dL, along with a cortisol >18 μg/dL after cosyntropin stimulation, and a 17-hydroxypregnenolone/ cortisol ratio >10 standard deviations above normal[24]. Non-classic 11OHD is diagnosed when 11-deoxycortisol reaches concentrations >1,800 ng/dL and cortisol is >18 μg/dL after cosyntropin[25]. Modestly abnormal baseline and even cosyntropin-stimulated steroid ratios can be deceiving, especially when immunoassays are used, and diagnostic confirmation with genetic testing is preferred for these very rare forms of CAH.

5.2 Androgen excess in CAH

Aside from its diagnostic significance, the excess 17OHP serves as substrate for fully functional enzymes, resulting in overproduction of adrenal androgens and precursors (Figure 1). This includes androstenedione (A4) and testosterone (T), as well as their 11-oxygenated metabolites, also called 11-oxyandrogens[26]. T and A4 are produced both by the gonads and adrenal glands, which might explain their poor correlation with clinical evidence of androgen excess in CAH patients[27,28]. In contrast, the major source of 11-oxyandrogens is the adrenal gland[29], which expresses CYP11B1 abundantly[30]. In fact, 11-hydroxyandrostenedione (11OHA4) is the most abundant unconjugated C_{19} steroid produced by the healthy human adrenal gland[31], and its synthesis is further enhanced in patients with classic[32] and non-classic 21OHD[23]. The downstream metabolites of 11OHA4, 11-ketoandrostenedione (11KA4) and 11-ketotestosterone (11KT), are produced primarily in periphery.

In vitro studies have shown that 11KT is a bioactive androgen, with maximum androgen potency comparable with that of T[33,34]. Several lines of evidence also support the androgenic bioactivity of 11KT *in vivo*. 11KT has been associated with physiological and premature adrenarche, and its concentrations exceed those of T prior to puberty[33]. 11-oxyandrogens are 3- to 4-fold higher in patients with classic CAH relative to age and sex-matched controls[32]. Higher concentrations of 11-oxyandrogens have been associated with higher adrenal volume, presence of testicular adrenal rest tumors (TARTs), and menstrual

irregularities in patients with classic CAH[35]. In addition, while in women with classic CAH, 11KT and T correlate directly, suggesting their common adrenal source, T correlates inversely with 11KT in sexually mature males with classic 21OHD,[32] pointing towards hypothalamic-pituitary-gonadal axis suppression by excessive adrenal androgens in uncontrolled patients.

In a recent study of 86 patients undergoing testing for NCCAH, 11-oxyandrogens were disproportionately elevated relative to conventional androgens in patients with confirmed NCCAH vs. those without CAH, 50% of whom had PCOS[36]. In contrast, A4 and T were similar between the two groups, reinforcing that the clinical utility of these traditional androgens in assessing the source of hyperandrogenism is limited Generally, a high A4/T ratio is suggestive of adrenal androgen excess.[37] To further complicate things, however, women with CAH often secondarily develop PCOS[38], and, conversely, a large subset of women with PCOS have increased adrenal androgen production.[39,40]

6. Management

The goal of treatment in patients with NCCAH is to suppress the excess adrenal androgen synthesis and the associated complications. Unlike patients with classic CAH, patients with NCCAH do not have adrenal insufficiency and do not need hormonal replacement with glucocorticoids. In children with precocious puberty or accelerated growth velocity, glucocorticoids may be used to suppress the ACTH-driven adrenal androgen excess[2]. Consideration for glucocorticoid discontinuation should be given once these children have attained their final adult height or two to three years post-menarche for girls[2].

For adolescents and adult women presenting with signs of hyperandrogenism, such as acne or hirsutism, oral contraceptive therapy (OCs) with estrogen-progestin preparations are the treatment of choice.[41] Treatment with OCs reduces hyperandrogenemia by a) suppression of LH and subsequently of ovarian androgen production; b) stimulation of hepatic synthesis of sex hormone-binding globulin, with resultant reduction of free androgen concentration; c) slight reduction of adrenal androgen synthesis; d) decreased binding of androgens to their receptors; e) increased clearance of testosterone; and f) mild inhibition in the pilosebaceous unit of 5α-reductase, the enzyme catalyzing conversion of testosterone to the most potent androgen, dihydrotestosterone (DHT)[41]. OCs containing progestins with low androgenicity like norgestimate, desogestrel, and gestodene might have an advantage over levonorgestrel over metabolic risk factors[41]. While norgestimate is the only available progestin with low androgeneicity that does not enhace the risk of venous thromboembolism over earlier generation progestins, evidence to support higher effectiveness of a particular OC for treating hirsutism is lacking. Women who present with hirsutism should be counselled about the expected time frame for improvement, which may take as long as 6–12 months,[41] and the potential need for adjunct direct hair removal methods, like photoepilation or electrolysis.

Addition of anti-androgens can be considered if results are unsatisfactory with OCs alone. These therapies should never be used in reproductive age women without reliable contraception methods, due to their potential effects on the developing male genitalia *in*

utero. Spironolactone, primarily a mineralocorticoid antagonist, also has anti-androgenic effects.[42] Other therapies for hirsutism include finasteride, a 5α-reductase inhibitor; or cyproterone acetate (CPA), a progesterone derivative that competes with DHT for binding to androgen receptor (not available in the US). Flutamide, a non-steroidal androgen receptor blocker is not recommended due to hepatotoxicity. Both spironolactone and finasteride have similar efficacy in improving hirsutism, with a pooled weighted mean difference of −7.02 [95% CI (−11.51 to −2.52)] Ferriman-Gallway units in comparison to placebo[41,43] and their effect is additive to that of OCs, further reducing hirsutism pooled weighted Ferriman-Gallway units by −1.73 [95% CI (−3.32 to −0.13)][43]. Glucocorticoids are the mainstay of androgen suppression therapy only in classic CAH. Although glucocorticoids were shown to be more effective than OCs or antiandrogens for suppressing serum adrenal androgen concentrations in women with NCCAH, they were less effective in improving hirsutism[44,45], with an increased risk of toxicity Thus, glucocorticoids are only used for managing hirsutism in female patients with NCCAH when intolerance to OCs and/or anti-androgens has been established[41].

Monitoring treatment of patients with NCCAH relies mostly on clinical evaluation, as reliable tests have been lacking. When elevated, T and A4 should be normalized, while 17OHP elevations should be permissible. Normalization of 17OHP typically indicates overtreatment with glucocorticoids. Interestingly, elevations of 11-oxyandrogens have been reported in a subset of women with PCOS relative to healthy controls[46,47]. Nevertheless, limited data suggests that these steroids might be higher in patients with NCCAH[48]. Although some commercial laboratories offer 11KT measurement, further studies are needed to clarify the clinical utility of 11-oxyandrogens as biomarkers of adrenal *vs*. gonadal over-activity. Standardized protocols, with testing that accounts for circadian rhythmicity and that directly compares women with NCCAH and PCOS will be essential to promulgate 11-oxyandrogens into future practical applications.

Pregnancy in women with NCCAH

For women with NCCAH with irregular and or anovulatory cycles who are interested in conceiving, glucocorticoids are the first-line therapy[49]. Ovulation induction with clomiphene citrate, followed by other reproductive endocrinology interventions are recommended when pregnancy is not achieved during treatment with glucocorticoids[50].

Limited evidence suggests that treatment with glucocorticoids might be reduce the time to conception and the risk of miscarriages in women with NCCAH, which occur at higher rates in this population as compared with healthy women[2,11,12,51]. Hydrocortisone, prednisone, or prednisolone are all safe to use in women attempting pregnancy, while dexamethasone, which is not inactivated by the placenta, should be avoided, due to risk of fetal hypothalamic-pituitary-adrenal axis and growth suppression[2]. Women with NCCAH who become pregnant spontaneously, without treatment with glucocorticoids, do not need to be treated with glucocorticoids.

Maternal 17OHP and androstenedione are elevated during pregnancy and cannot be used as biomarkers of CAH control. Hence, pregnant women should be followed clinically. Guidelines are lacking in regards to the optimal management of women with NCCAH

during pregnancy. Some practices continue low doses of glucocorticoids thoughout pregnancy if used pre-conception, while others stop glucocorticoids once pregnancy is confirmed or after the first trimester.

Summary and conclusions

NCCAH is a relatively common disease, and it should be suspected and excluded in all women with PCOS-like phenotype, including hirsutism, acne, and menstrual abnormalities. Other non-classic forms of CAH that might mimic PCOS, such as HSD3B or CYP11B1 deficiencies, are extremely rare. Screening with 17OHP, followed by a confirmatory cosyntropin stimulation test if needed, establishes the diagnosis of 21OHD. Because hormonal cutoffs can be ambiguous, in part due to the low numbers, along with immunoassay artefacts, genetic testing is often indicated to confirm the very rare HSD3B or CYP11B1 deficiency when suspected based on clinical and hormonal abnormalities. Although the prevalence of PCOS far exceeds that of CAH, and although overlap in management exists (particularly for hirsutism and acne), treatment of infertility and pre-conception considerations warrant accurate diagnosis. Biomarkers indicative of adrenal as opposed to gonadal androgen excess, such as 11-oxyandrogens, might facilitate the management of patients with hyperandrogenism; studies directly comparing patients with CAH and PCOS are lacking, and will be key to translating pathophysiology knowledge into clinical applications.

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Figure 1 was created using Biorender.com.

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Key Points

- Non-classic congenital adrenal hyperplasia (NCCAH) has an overall prevalence of 1:200 in the US population and up to 1:30 in certain ethnic groups, particularly Mediterraneans and Ashkenazi Jews.
- 21-hydroxylase deficiency accounts for 95% of CAH cases.
- Patients with NCCAH do not have adrenal insufficiency and do not need hormonal replacement.
- Glucocorticoids can be used in children with NCCAH who present with precocious puberty in order to suppress the adrenal androgen excess; the need for therapy should be reassessed after final height is attained.
- Hormonal screening for NCCAH with 17-hydroxyprogesterone is indicated in all patients with polycystic ovarian syndrome (PCOS)-like phenotype, as the two cannot be distinguished clinically.
- The treatment of women with NCCAH who present with signs of hyperandrogenism and who are not planning pregnancy is similar to those with PCOS, and includes oral contraceptives +/− anti-androgen therapy. Treatment of infertility, however, starts with glucocorticoids in non-classic CAH women.
- Research suggests that steroid biomarkers of primarily adrenal origin, such as 11-hydroxyandrostenedione and its downstream bioactive metabolite 11-ketotestosterone, may offer guidance regarding disease control and management in non-classic CAH.

Synopsis

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic defects in cortisol synthesis. The altered negative feedback of cortisol to the hypothalamus and the pituitary gland prompts corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) elevations. Increased ACTH, in turn, has two downstream effects: 1) it overstimulates adrenal steroidogenesis, resulting in an accumulation of steroids above the enzymatic blockage; and 2) when sustained, ACTH elevation promotes adrenal gland enlargement (hence, the term CAH).

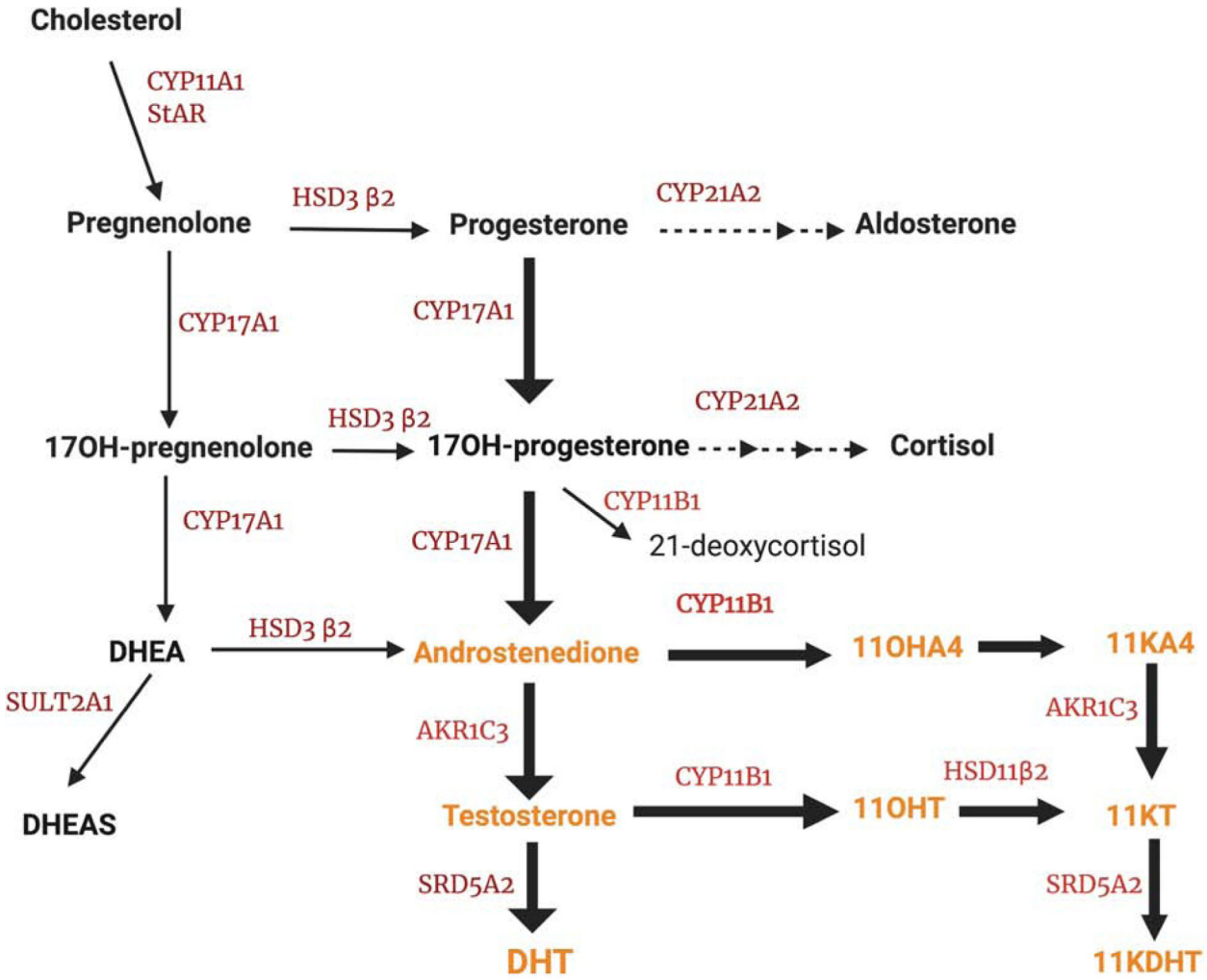

Figure 1 : Steroidogenic pathway

Genetic defects in 21-hydroxylase result in accumulation of 17α-hydroxyprogesterone, which is diverted towards androgens, including: androstenedione, testosterone, and 11-oxygenated androgens (11OHA4 and 11OHT); the latter two are oxidized to 11KA4 and 11KT, respectively, in the kidneys and other tissues.

Abbreviations: StAR: steroidogenic acute regulatory protein; CYP11A1, cholesterol side-chain cleavage; HSD3β2, 3β-hydroxysteroid dehydrogenase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYB5A, cytochrome *b*5 type A; CYP11B1, 11β-hydroxylase; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; HSD11B2, 11β-hydroxysteroid dehydrogenase, type 2; SULT2A1, sulfotransferase 2A1; SRD5A2, steroid 5α-reductase type 2; DHEA: dehydroepiandrosterone; DHEAS: dehydroepiandrosterone sulfate; 11OHA4: 11β-hydroxyandrostenedione; 11OHT: 11β-hydroxytestosterone; 11KA4: 11-ketoandrostenedione; 11KT: 11-ketotestosterone;.

Table 1:

Uncommon Causes of Congenital Adrenal Hyperplasia (CAH)

Side chain cleavage (SCC) deficiency:	
Prevalence:	• rare, relatively increased prevalence in Southeastern Turkey[52] • first described in 2001
Presentation:	• severe, early onset adrenal failure in infancy • minimal aldosterone synthesis with high plasma renin • 46, XY with female external genitalia but no cervix, uterus and fallopian tubes and well-developed Wolffian duct derivatives • 46, XX have normal genitalia at birth
Diagnosis:	• deficiency of all steroid hormones • absent response to cosyntropin or hCG stimulation • clinically and hormonally indistinguishable from lipoid CAH but atrophic adrenals and gonads • genetic testing needed to differentiate lipoid CAH and SCC deficiency
Non-classic form:	• mutations wherein 10–20% enzyme activity is retained • clinically and hormonally indistinguishable from non-classic lipoid CAH
Management:	• physiological replacement of GC • supplementary salt in newborns with MC replacement thereafter • discussion regarding orchiectomy in 46, XY patients
StAR deficiency: Lipoid CAH	
Prevalence:	• rare, with >100 patients reported; • second most common form of CAH in Korea and Japan[52]
Presentation:	• most severe steroidogenic disorder; most present with neonatal crisis; rarely, presentations up to age 1 year[15] • minimal aldosterone synthesis with high plasma renin • 46, XY with female external genitalia but no cervix, uterus and fallopian tubes but well-developed Wolffian duct derivatives, consistent with some StAR-independent T synthesis early in life • 46, XX have normal genitalia at birth and go through puberty with breast development and cyclic vaginal bleeding; anovulatory cycles as progesterone synthesis disturbed • impaired DHEA synthesis eliminates feto-placental estriol production
Diagnosis:	• deficiency of all steroid hormones • absent response to cosyntropin or hCG stimulation • grossly enlarged adrenals • genetic testing needed to differentiate lipoid CAH and SCC deficiency
Non-classic form:	• associated with mutations that retain 20–30% activity • mildly compromised MC secretion • can present from toddlers to adulthood with mild adrenal insufficiency • wide variation in gonadal function

	• 46, XY typically have normal-appearing external genitalia
Management:	• physiological replacement of GC • supplementary salt in newborn, MC replacement thereafter • discussion regarding orchiectomy in 46, XY patients
HSD3B2 (Δ^5- Δ^4 Isomerase) deficiency	
Prevalence:	• very rare (<0.5% of all CAH); < 1 in 1,000,000[53]
Presentation:	• both gonads and adrenal glands affected • 46, XX may have atypical genitalia due to large amounts of DHEA, some of which is converted to T by extra-adrenal HSD3B1 • 46, XY can have severe hypospadias, micropenis, bifid scrotum and undescended testis due to inadequate T. In contrast with 21OHD, it is diagnosed earlier and more frequently in males, and females can remain undiagnosed.
Diagnosis:	• basal or cosyntropin-induced rise in Δ^5 steroids typically 17α-hydroxypregnenolone to ≥3000 ng/dL (90 nmol/liter). • 17OHP4 can be high due to activity of extra-adrenal HSD3B1 • molecular genetic testing recommended to confirm diagnosis
Non-classic form:	• controversial if non-classic forms exist
Management:	• GC and MC replacement • patients may need higher GC doses[53] as hyperandrogenemia from accumulation of DHEAS can be difficult to control • discussion regarding surgical correction of atypical genitalia • sex hormones for patients who fail to progress through puberty (few).
11β-hydroxylase deficiency	
Prevalence:	• second most common form of CAH (5–8% of all cases) • 1:100,000; higher prevalence (15% of CAH) in Middle Eastern population[54]
Presentation:	• adrenal insufficiency • 46, XX might have atypical genitalia and/or other signs of hyperandrogenism • precocious puberty in both sexes • low-renin hypertension due to excess DOC • newborns can have mild, transient salt loss due to resistance to MC in infancy
Diagnosis:	• excess 11-deoxycortisol and DOC • may be detected on newborn screening, as 17OHP4 might be sufficiently elevated
Non-classic form:	• rare[16]
Management:	• GC replacement at doses similar to 21OHD • mineralocorticoid receptor antagonits
CYP17A1 deficiency (both 17α-hydroxylase deficiency and 17,20 lyase deficiency)	

Prevalence:	• 1: 50,000; increased frequency in Brazil (second most common form after 21OHD)[55] due to presence of a founder mutation
Presentation:	• both gonads and adrenals affected • impaired cortisol and sex steroid synthesis; aldosterone synthesis unaffected. • corticosterone excess compensates for cortisol deficiency • excess DOC accumulation results in low-renin hypertension • hyper-gonadotropic hypogonadism • 46, XX are normal at birth but may not undergo adrenarche or puberty • 46, XY have undervirilized external genitalia • patients can have low bone mineral density even in absence of GC therapy[56]
Diagnosis:	• elevated DOC, corticosterone, 18-OH-corticosterone and 18-OH-DOC and low concentrations of 17-hydroxylated steroids, which respond poorly to cosyntropin[15]
Non-classic form:	• not defined although phenotypic variability occurs
Management:	• GC to suppress ACTH and excess mineralocorticoids • age and gender-appropriate sex-steroid replacement, if necessary
Isolated 17,20-lyase activity	
Prevalence:	• extremely rare
Presentation:	• can be caused by mutations in several different genes – specific mutations in the “redox partner-binding site” or the catalytic active site of CYP17A1 – cytochrome *b*5 (a protein that interacts with CYP17A1 to promote 17,20 lyase activity) deficiency leading to androgen deficiency with associated methemoglobinemia – rare mutations in the electron-donating domain of POR • both gonads and adrenal glands affected • all reported patients so far are 46, XY likely due to ascertainment bias[52]
Diagnosis:	• normal 17-hydroxycorticosteroids but markedly reduced sex steroids (DHEA, DHEAS, androstenedione, T, DHT)
Non-classic form:	• not reported
Management:	• age and gender-appropriate sex-steroid replacement, if necessary
P450 oxidoreductase (POR) deficiency	
Prevalence:	• incidence and phenotype varies with ethnicity but fairly common[15] • POR gene is highly polymorphic • relatively newly recognized form of CAH, first described in 2004[57]
Presentation:	• characterized by partially deficient CYP17A1, with or without associated deficient activity of 21-hydroxylase and aromatase • newborns often have associated skeletal defects called Antley-Bixler syndrome (ABS), characterized by craniosynostosis, radio-ulnar or radio-humeral synostosis, midface hypoplasia and other skeletal manifestations. ABS may be seen in conditions other than CAH. • great variability in clinical and hormonal findings; • atypical genitalia in both sexes

	– incompletely developed external genitalia in affected males due to defective testicular steroidogenesis – phenotype in females varies with mutation; alternative “backdoor pathway” of androgen synthesis leads to excess synthesis of active androgens and result in atypical genitalia in 46, XX • defective placental aromatase activity in some mutations permits fetal androgenic precursors to enter and virilize the mother during pregnancy similar to women carrying a fetus with aromatase deficiency
Diagnosis:	• near normal cortisol levels common which respond poorly to cosyntropin • usually have normal electrolytes and mineralocorticoid function • high concentration of 17OHP4 that responds variably to cosyntropin; some patients might be detected by newborn screening • increased pregnenolone, progesterone, DOC and corticosterone • low levels of adrenal precursors of sex steroids like DHEA, androstenedione • abnormal elevations of metabolites from “backdoor pathway”
Non-classic form:	• few patients diagnosed in newborn period
Management:	• adrenal insufficiency present in the majority of patients, cosyntropin test recommended for diagnosis[58] • sex-hormone replacement at pubertal age

GC, glucocorticoids; MC, mineralocorticoids; 17OHP4, 17α-hydroxyprogesteronel; T, testosterone; DOC, 11-deoxycorticosterone; StAR, steroidogenic acute regulatory protein; HSD3B2/1, 3β-hydroxysteroid dehydrogenase type 1/2.

Data from Refs 15, 16, 52–58.