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The Next 150 Years of Congenital Adrenal Hyperplasia

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Abstract

Congenital adrenal hyperplasias (CAH) are a group of autosomal recessive defects in cortisol biosynthesis. Substantial progress has been made since the description of the first report, 150 years ago. This article reviews some of the recent advances in the genetics, diagnosis and treatment of CAH. In addition, we underline the aspects where further progress is required, including, among others, better diagnostic modalities for the mild phenotype and for some of the rare forms of disease, elucidation of epigenetic factors that lead to different phenotypes in patients with identical genotype and expending on treatment options for controlling the adrenal androgen excess.

1. Introduction

In a recent issue of *Endocrinology*, Luisa Delle Piane and colleagues put the spotlight on the case regarded as the first report of non-salt wasting congenital adrenal hyperplasia (CAH), initially described in 1865 by Luigi de Crecchio[1]. The article details the autopsy of a prematurely deceased virilized female with enlarged adrenal glands, and the conundrum it presented to the team of pathologists involved[2]. Much has been learned over the past 150 years about CAH, now recognized as one of the most common inherited diseases. However, contemporary practitioners and researchers still have questions to answer and hypotheses to test even in the modern medical era. In this article, we focus on the recent advances in CAH and on those aspects where progress over the next century is imperative.

2. Congenital adrenal hyperplasia-brief overview

CAH is an umbrella term for inherited enzymatic deficiencies in cortisol synthesis (Figure 1). The defective cortisol production alleviates the negative feedback to the hypothalamus and pituitary gland, resulting in excessive secretion of corticotropin-releasing hormone (CRH) and adrenocorticotropin (ACTH), respectively. The raised ACTH, in turn, cannot

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overcome the block in cortisol synthesis, but its trophic action leads to enlargement of the adrenal glands. The enzymatic defects in all forms of CAH can be complete or partial, resulting into a broad spectrum of clinical presentations. The most severe forms are conventionally called “classic” CAH and are the easiest to recognize. Conversely, the milder forms or “nonclassic” CAH are often difficult to diagnose or may be overlooked, as their features overlap between each other, as well as with other clinical entities.

The most common form of CAH is 21-hydroxylase (P450c21, CYP21A2) deficiency (21OHD, Table 1), accounting for over 90% of all cases[3]. Classic 21OHD affects approximately 1 in 16,000 newborns worldwide[4]. Nonclassic 21OHD occurs in roughly 1 of 1,000 Caucasians and even more frequently in populations of specific ethnicities, such as Ashkenazi Jews (1:27), Hispanics (1:53), Yugoslavs (1:62) and Italians (1:300)[5]. Complete absence of CYP21A2 activity results in both glucocorticoid and mineralocorticoid deficiencies, as well as in severe adrenal-derived androgen excess. The androgen excess is clinically evident in newborn girls, whose external genitalia are virilized. Patients with nonclassic 21OHD do not have adrenal insufficiency, and they typically present with evidence of androgen excess, such as premature pubarche, hirsutism, acne, and irregular menses, at various ages.

A second form of CAH is 11β-hydroxylase (CYP11B1) deficiency (11OHD), which represents up to 5–8% of all CAH cases in some series of high-risk populations[6,7], although the incidence of this disorder in the general population has never been ascertained. Its incidence is estimated at 1 in 100,000 live births in the general population but is 20 times higher in Moroccan Jews, due to a founder mutation[8]. CYP11B1 catalyzes the conversion of 11-deoxycorticosterone (DOC) and 11-deoxycortisol into corticosterone and cortisol, respectively, reactions whose substrates are products of CYP21A2. As in 21OHD, patients exhibit decreased cortisol synthesis and adrenal androgen overproduction. In contrast to 21OHD, the distinctive features of classic 11OHD are hypertension and less commonly hypokalemia, owing to the mineralocorticoid action of DOC, which manifests in two-thirds of patients often in mid-childhood and also makes patients with 11OHD less prone to adrenal crisis than those with 21OHD. Nonclassic 11OHD is difficult to distinguish clinically from nonclassic 21OHD but is far less common.

A third form of CAH is 3β-hydroxysteroid dehydrogenase/isomerase type 2 (3βHSD2) deficiency and is characterized by both mineralo- and glucocorticoid deficiency. This enzyme catalyzes the reactions preceding those of CYP21A2, being responsible for the C3 dehydrogenation and simultaneous Δ^5 to Δ^4 transfer of the double bond into the A ring of the core steroid structure. Humans have 2 homologous 3βHSD enzymes: type 1, expressed in placenta and peripheral tissues (skin, prostate and breast), and type 2, expressed in the adrenal glands and gonads[9–11]. Severe impairment of 3βHSD2 results in both mineralocorticoid and glucocorticoid deficiencies and limits steroid flux to dehydroepiandrosterone (DHEA). In peripheral tissues containing 3βHSD1 and downstream enzymes, DHEA is metabolized to androgens, which causes mild virilization in newborn girls, such as slight clitoral enlargement without the labioscrotal fusion found in 21OHD and 11OHD. In contrast with the latter two, boys are undervirilized, due to the impaired androgen synthesis in the testes, which also requires 3βHSD2. In women, nonclassic 3βHSD deficiency was thought to be common but is actually extremely rare, and most children with premature adrenarche do not have a mutation in the *HSD3B2* gene (see section 3.1 and 3.2.2). Nonclassic 3βHSD deficiency is difficult to distinguish from nonclassic 21OHD and 11OHD or PCOS clinically, all presenting with hirsutism and oligomenorrhea.

Deficiency of 17α-hydroxylase/17,20-lyase (CYP17A1) is rare, with most cases described coming from Brazil and Asia. CYP17A1 is required for both cortisol and androgen synthesis. The only unaffected pathway is that to progesterone, aldosterone and other mineralocorticoids, and the weak glucocorticoid corticosterone, similar to the rodent adrenal that lacks this enzyme. In order to produce enough corticosterone to substitute for cortisol, DOC rises markedly, and patients present with hypertension, hypokalemia and hypogonadism. Both 46,XY and 46,XX individuals have feminine external genitalia and primarily present during pubertal age, with amenorrhea and absence of secondary sexual characteristics. Occasionally, 46,XY cases of 17OHD are diagnosed in infancy due to inguinal hernias. Partial defects of CYP17A1 activities have been found in women with poor breast development and/or menstrual abnormalities[12, 13] and in males with ambiguous external genitalia, absence of male secondary sexual characteristics, and gynecomastia at puberty[14], but a "nonclassic" form has not been described. Conceivably, patients with very mild or nonclassic 17OHD might be dismissed as having low-renin hypertension and primary hypogonadism and never evaluated for 17OHD. Isolated 17,20-lyase deficiency has been described in patients with mutations in the *CYP17A1*[15,16], *POR*[17] or *CYB5A*[18,19] genes, but these patients do not have CAH because cortisol synthesis is normal. Isolated 17,20-lyase deficiency can be difficult to distinguish from partial androgen insensitivity or from rare steroidogenic defects such as AKR1C2+AKR1C4[20].

Lipoid CAH (LCAH), the most severe defect in steroidogenesis, is named for the massively enlarged, lipid-laden adrenals characteristic of this disease. LCAH is caused by a defect in the steroidogenic acute regulatory protein (StAR), which prevents the mobilization of cholesterol into steroidogenic pathways and results in negligible production of all steroids. Cholesterol side-chain cleavage enzyme (P450scc) deficiency yields a similar severe global defect in steroidogenesis as LCAH but without the enlarged adrenals found with StAR deficiency[21,22]. Affected children typically present with life-threatening adrenal insufficiency in early infancy, and males appear phenotypically female due to impaired testicular androgen synthesis in utero. Nonclassic forms of both lipoid CAH and P450scc deficiency have been described, presenting with late-onset isolated glucocorticoid insufficiency and normal external genitalia[23–26].

Finally, P450-oxidoreductase (POR) deficiency combines features of 21OHD, 17OHD, and aromatase (CYP19A1) deficiencies, in various combinations and severities[27]. In addition, these patients may present skeletal malformations, such as craniosynostosis, radiohumeral or radioulnar synostosis, and femoral bowing, as part of the Antley–Bixler syndrome[28]. In contrast, one of the initial cases described was a phenotypically normal woman with infertility, illustrating the wide spectrum of this disease and suggesting "nonclassic" disease could be defined by the absence of skeletal and/or genital anomalies.

3. Diagnosis of CAH

3.1. Hormonal testing

For each enzymatic defect, the precursor to product ratio is the mainstay of diagnosis. Cosyntropin stimulation maximizes these ratios and is particularly important for all cases with indeterminate baseline results[29].

Newborn screening for 21OHD was first implemented in 1978[30,31], and is currently available throughout the United States and many other countries. Screening reduces the time to diagnosis in infants, particularly for boys who are often not diagnosed at birth and suffer crises several days later[32,33]. The most important role of early diagnosis is to reduce morbidity and mortality for severely affected babies, although this aspect remains controversial and might also depend on the economic and healthcare status of each country[34–36]. First-tier testing measures 17OHP in dried blood spots by an immunoflurometric assay. A random 17OHP >20,000 ng/dL is suggestive of 21OHD; however, false-positive results are commonly seen in premature and severely ill infants[37,38]. Factors contributing to false-positive screening include activation of the hypothalamic-pituitary-adrenal axis in response to perinatal stress, the relative immaturity of adrenal CYP11B1 activity in preterm infants[39], which also elevates 17OHP[39,40], and interfering steroids in the immunoassays. False-negative rates of up to 22% have been reported in infant screening[41,42], particularly when mothers had been exposed to glucocorticoids prenatally. Although higher false-negative rates have been reported in girls[42], it is possible that boys not identified with newborn screening remained undiagnosed for several years. Weight- and gestational age-adjusted cutoffs for 17OHP have been implemented to improve the positive predictive value of screening,[43–45] and more specific second-tier screening procedures to adjudicate abnormal first-tier screens have been successfully implemented in some states[46]. Beyond neonatal screening, children with clinical evidence of androgen excess—such as pubic and axillary hair growth, oily skin, rapid somatic growth, and advanced skeletal maturation— initially undergo testing of a morning baseline 17OHP[47]. Intermediate screening values (200–1000 ng/dl) are followed by retesting after cosyntropin stimulation. The diagnosis of classic 21OHD is based on stimulated 17OHP levels above 10,000 ng/dl, while nonclassic 21OHD requires a 17OHP >1,000 ng/dl[47].

Classic 11OHD and 3βHSD2 deficiency overlap clinically with classic 21OHD, and in all 3 conditions, 17OHP can be elevated. Due to their low prevalence, the diagnosis of 11OHD is considered when hypertension and/or hypokalemia are present, or when the 17OHP is lower than expected for the degree of androgen excess in a 21OHD patient. 3βHSD2 deficiency is considered if virilization is mild relative to the degree of salt wasting. Nonclassic 21OHD is vastly more common than other forms of nonclassic CAH, but these conditions are even more difficult to distinguish clinically than their classic forms. A diagnosis of nonclassic 11OHD or 3βHSD2 deficiencies should be pursued in patients with androgen excess during childhood only after more common causes (such as exposure to exogenous androgens, PCOS, 21OHD, adrenal or gonadal tumors, chorionic gonadotropin-secreting tumor) have been excluded. Nonclassic 11OHD is diagnosed when 11-deoxycortisol rises above 1,800 ng/dl and cortisol is >18 μg/dl after cosyntropin[7]. The diagnosis of nonclassic 3βHSD deficiency requires a 17-hydroxypregnenolone >3,000 ng/dl and a cortisol >18 μg/dl after cosyntropin, with a 17-hydroxypregnenolone/cortisol ratio >10 standard deviations above normal[48].

In most centers, steroid measurements are performed by immunoassays, which are limited by cross-reactivity and can yield unreliable results, particularly when ordinarily minor steroids are markedly elevated. More accurate testing can be attained by using liquid chromatography/tandem mass spectrometry (LC-MS/MS)[49–51]. In addition to increased specificity and sensitivity, LC-MS/MS also affords quantitation of multiple steroids in a single measurement. Elevated 21-deoxycortisol by LC-MS/MS has been shown to increase the sensitivity of newborn screening[50] and to discriminate heterozygote carriers of CYP21A2 mutations from nonclassic 21OHD better than 17OHP[52]. Simultaneous measurement of 11-deoxycortisol can distinguish 11OHD from 21OHD in second-tier screening. Other novel biomarkers for diagnosis, such as 16α-hydroxyprogesterone and 11β-hydroxyprogesterone, have been recently proposed (Fig. 2)[53]. Multi-steroid panels simultaneously testing all forms of CAH clinically in question from a small volume serum sample will likely dominate in the future. For now, however, the widespread use of LC-MS/MS is constrained by its limited availability, technical demands and high cost. Alternatively, comprehensive analysis of urinary steroid metabolites using gas chromatography-mass spectrometry (GC/MS) affords patterns characteristic for each form of CAH[54]. While GC/MS has been used for decades, the availability of this methodology is limited, and sample throughput is slow and tedious.

3.2. Genetics of CAH and role of genetic testing

3.2.1. Genetics of CAH—All CAH forms are monogenic, autosomal-recessive disorders. The gene encoding human CYP21A2 is located on chromosome 6p21.3, within the human leucocyte antigen (HLA) major histocompatibility complex and adjacent to the genes for the fourth component of complement[55–57]. In addition to this active gene, humans also have a 98% homologous pseudogene (*CYP21A1P*), situated within 30 kb, which encodes a truncated, inactive enzyme. Most of the mutant 21OHD alleles occur by intergenic recombinations and gene conversion between the two CYP21A genes[58]. Mutations that result in complete or nearly complete compromise of 21-hydroxylase activity (such as complete deletions, large gene conversions, and non-sense or frame-shift mutations), typically result in classic 21OHD. Nonclassic 21OHD alleles preserve up to 20–30% of the enzyme activity, which is sufficient for adequate cortisol and aldosterone production. A strong genotype-phenotype correlation exists for classic 21OHD; however, the clinical manifestations of nonclassic disease are quite variable, suggesting that other factors (genetic, epigenetic or environmental) may affect the phenotypic expression[58]. The elucidation of these additional factors is an important priority for future CAH research. The human 11-hydroxylase (*CYP11B1*) gene comprises nine exons and encodes a protein of 503 amino acids.

The *CYP11B1* gene is located on chromosome 8q21-22, approximately 40 kb apart from the highly homologous aldosterone synthase gene (*CYP11B2*)[59]. Over 80 mutations have been described to date, the majority of which are associated with classic 11OHD[60–72]. Relatively few mutations associated with nonclassic 11OHD have been identified[72–76], most over the recent years. Earlier studies on women with androgen excess failed to identify mutations in the *CYP11B1* gene, even in the presence of elevated precursor 11-deoxycortisol[76]. The relationship between genotype and phenotype remains unclear; for example, blood pressure correlates poorly with serum DOC concentrations.

The *HSD3B2* gene, located on chromosome 1p13.1, is expressed almost exclusively in the adrenal and gonads[10]. The highly homologous type I 3βHSD gene (*HSD3B1*) is located in vicinity on the same chromosome, but it is expressed in placenta and peripheral tissues, such as skin, breast and prostate[77]. The *HSD3B2* gene consists of four exons, of which exons 2–4 are translated into a protein of 371 amino acids[77]. In proximity reside 5 pseudogenes (HSD3Bψ1–5); two of these pseudogenes (ψ1 and ψ2) separate the two expressed *HSD3B1* and *HSD3B2* genes, preventing them from sharing common promoter elements[78]. Thus, *HSD3B1* is usually intact in patients with 3βHSD2 deficiency, explaining why serum concentrations of some Δ^4 steroids can be normal or even elevated in these patients[79]. A strong genotype-phenotype correlation exists. Nonsense and frame-shift mutations that ablate enzyme transcription or function result in salt-wasting forms of 3βHSD2 deficiency. Conversely, single amino-acid substitutions that moderately decrease the affinity of the enzyme for substrate or cofactors lead to non-salt-wasting forms of 3βHSD2 deficiency[80–84]. However, some mutations, like A82T or T259M, have been associated with phenotypic heterogeneity[77].

Although human CYP17A1 catalyzes two separate reactions, it is encoded by a single gene located on chromosome 10q24.3, which consists of 8 exons and encodes a 508-amino-acid protein[85–87]. Over 90 CYP17A1 mutations have been described throughout the entire gene. Populations in which 17OHD is more prevalent, such as Brazilians[88], Canadian Mennonites, Dutch Frieslanders[89], Japanese[90], and patients from East Asia[91], however, have specific reoccurring mutations, due to founder effects. Rare mutations located in the redox-partner interaction site or active site can lead to isolated 17,20-lyase deficiency[15,16,92,93].

3.2.2. Clinical use of genetic testing—The role of genetic testing is best established in cases that remain equivocal after cosyntropin stimulation or for prenatal genetic counseling. Up to 70% of patients with nonclassic 21OHD carry a classic 21OHD mutation on one of their alleles, rendering them a carrier for classic 21OHD[94, 95]. Children of women with nonclassic 21OHD have an approximately 2.5% risk of being born with classic 21OHD and a 15% risk for having nonclassic 21OHD[96]. The same increased risk of 21OHD theoretically applies equally to fathers with nonclassic 21OHD, but similar data for men are lacking. The risk increases significantly in ethnic groups known to have a higher prevalence of the disease[96]. Thus, particularly in cases of a known affected prospective parent, preconception genetic testing of the second parent might help families to understand the risk of an affected offspring and to receive appropriate genetic counseling.

Another role for genetic testing evolved from efforts to prevent virilization of female fetuses affected with classic 21OHD. Prenatal treatment of the mother carrying an affected child with dexamethasone can reduce genital virilization compared to sisters who were not treated in utero. Prenatal diagnosis of 21OHD has been accomplished by chorionic villus sampling at approximately 14 weeks of gestation or by amniocentesis at approximately 20 weeks[97]. Both approaches are invasive and increase the risk of miscarriages[98–100]. To be successful, however, dexamethasone treatment must be started by 8 weeks' gestation, when genital anatomy is sensitive to dihydrotestosterone action[101, 102]. Thus, presumptive treatment must be started before the prenatal diagnosis can be established. Statistically, only 1 in 8 fetuses is an affected girl, so up to 88% of pregnancies are treated unnecessarily. Prenatal dexamethasone was associated with impaired verbal working memory and related cognitive metrics in one study,[103] and more recent data have suggested that exposure to prenatal synthetic glucocorticoids interferes with the normal brain development[104,105]. Thus, prenatal therapy is currently regarded as experimental by academic societies[47,106].

In recent years, early noninvasive genetic testing has been proposed. Lo and colleagues first documented the presence of cell-free fetal DNA (cff-DNA) in the maternal circulation in 1997[107]. Quantitative polymerase chain reaction analysis of the SRY gene in maternal plasma was introduced in 2001, as a sensitive method for fetal gender determination in women with CAH[108]. Technological advances in genetic testing have recently made the diagnosis of 21OHD possible as early as 6 weeks of gestation, by targeted massively parallel sequencing performed on cff-DNA circulating in maternal plasma[109]. Rarely, prenatal DNA sequencing can lead to erroneous diagnosis of CAH, as in duplication of the *CYP21A2* gene[110]. Moreover, massively parallel sequencing remains technically challenging, costly and only available in selected centers.

As genetic testing becomes cheaper and more widely available, one can anticipate that targeted sequencing of several genes of interest could clarify the diagnosis in patients with atypical clinical presentations and borderline biochemical workup. Diagnosis of all forms of CAH currently relies almost exclusively on hormonal testing, which is fraught with pitfalls. For example, earlier studies of hirsute women over-diagnosed nonclassic 3βHSD2 deficiency, when relying on measurement of Δ^5 steroids[111–114]. Genetic testing uncovered mutations in the *HSD3B2* gene in only a vanishingly small number of such women[48, 115]. As genetic databases continue to grow, more robust links between genotype and phenotype will develop. In the interim however, the clinical and biochemical context remain critical for the diagnosis of this heterogeneous group of diseases.

4. Treatment of CAH

4.1. Conventional and experimental glucocorticoid and mineralocorticoid therapy

The two general goals of treatment in all forms of CAH are to replace the deficient hormones on one hand, and to offset the undesirable effects of excessive hormonal production on the other. With a variety of available formulations, corticosteroid replacement has become relatively facile, with some limitations. For example, the aldosterone substitute fludrocortisone acetate is not available in mainland China; hydrocortisone tablets are not sold in many countries including Brazil; and liquid forms of hydrocortisone must be obtained from compounding pharmacies without quality control in the United States. Conversely, management of adrenal androgen excess in both classic and nonclassic CAH remains challenging. Several strategies to counteract the excessive adrenal androgen synthesis have been explored, as outlined below.

The most commonly used approach has been that of suppressing ACTH by strategic dosing of glucocorticoids. The typical short- or intermediate-acting glucocorticoid regimens, which are sufficient for replacement in non-CAH related adrenal insufficiency, often fail to blunt the early morning rise of ACTH, which is the principal drive for adrenal androgen overproduction. Physicians have resorted to supraphysiologic or non-physiologic (nocturnal) doses of glucocorticoids in an attempt to counteract the excessive androgen synthesis, thus promoting bone loss, obesity and features of metabolic syndrome in these patients[116,117]. Sustained-released hydrocortisone preparations have been recently developed, attempting to mimic the cortisol circadian rhythm and to suppress the early morning ACTH elevation[118,119]. In a phase two clinical trial, a modified-release formulation of hydrocortisone administered once daily mimicked the normal diurnal cortisol rhythm more closely than conventional hydrocortisone dosing; however, androstenedione rose higher than with conventional hydrocortisone in the afternoon. After reformulation, a second phase two trial with twice-daily dosing achieved lower hydrocortisone dose equivalent, as well as lower 17OHP and adrostenedione levels, compared to conventional therapies[118]. Continuous subcutaneous hydrocortisone infusion via a pump, mimicking a circadian secretory profile, has been used experimentally in young patients with increased cortisol clearance, and this approach was shown to decrease 17OHP and adrenal androgen production with a lower total daily dose[120,121].

4.2. Experimental therapies beyond glucocorticoids

Another alternative for decreasing ACTH was undertaken in a recent proof-of-concept single-blind, placebo-controlled, single center, fixed-sequence, single-dose trial study, using the corticotropin-releasing factor receptor type 1 antagonist NBI77860[122]. At 300 and 600 mg, a nocturnal dose lowered morning ACTH and 17OHP by >50% from baseline in 4 of 8 participants, and the action correlated with drug exposure. Further studies are needed to determine the effects of NBI77860 on key parameters of disease control such as serum androgens when given in repeated doses at steady state.

A second strategy is that of directly inhibiting androgen synthesis or antagonizing androgen action. The combination of flutamide, an antiandrogen, and testolactone, an aromatase inhibitor, permitted the use of lower doses of hydrocortisone and fludrocortisone acetate and normalized linear growth and bone maturation in children followed for 2 years[123,124]. Long-term results from this trial are anticipated soon; however, latter-generation anti-androgens and aromatase inhibitors have supplanted both flutamide and testolactone for the treatment of prostate and breast cancers, respectively. A GnRH antagonist has been successful in improving height in children with 21OHD and precocious puberty[125]. Abiraterone acetate, a potent CYP17A1 inhibitor approved for use in castration-resistant prostate cancer, normalized androstenedione in adult women with classic 21OHD and elevated androgens when added to physiologic hydrocortisone and fludrocortisone acetate replacement in one short-term study[126].

Monitoring and titrating treatment remains a major clinical challenge, and no consensus exists among practitioners. Although 17OHP has long been used to guide the management of 21OHD, its serum concentration correlates poorly with DHEA and androstenedione[127].

DHEAS, the major C_{19} adrenal product, can be paradoxically low in 21OHD patients with inadequate control[128–130]. Moreover, there is no good correlation between the routinely measured androgens (androstenedione and, in women, testosterone) and clinical evidence of androgen excess[131,132]. Research conducted in the recent years has brought into consideration non-conventional androgens and precursors, such as steroids derived from the so-called "back-door pathway"[133] (Figure 2). This pathway starts with two consecutive 5α-, then 3α- reductions of 17OHP and leads via androsterone and 5α-androstane-3α,17β-diol to dihydrotestosterone, the most potent endogenous androgen, while bypassing androstenedione and testosterone. Kamrath and colleagues found increased excretion of 5α-reduced products and intermediates of the backdoor pathway in 142 children and young adults with CAH, compared with 138 similarly aged controls, particularly during the first year of life[127]. Consequently, this pathway has been proposed to contribute to the virilization of female fetuses with 21OHD,[134] as has been shown in POR deficiency[135]. In addition, the adrenal glands also produce other active androgens, such as 11β-hydoxytestosterone. Substantial amounts of 11-oxygenated C_{19} steroids were documented in adrenal vein samples obtained from normal adrenals, with 11β-hydroxyandrostenedione being particularly abundant[136]. In a cell-based androgen transactivation assay, 11β-hydroxytestosterone and 11-ketotestostereone activated the androgen receptors at concentration approximately ten times higher than testosterone, but 30 times lower than androstenedione and 11β-hydroxyandrostenedione [136]. The contribution of these steroids to the androgen excess of 21OHD remains to be further investigated. As these 11-oxygenated C_{19} steroids are products of CYP11B1, an adrenal-specific enzyme, these compounds might serve as specific biomarkers of adrenal-derived androgen excess and facilitate titration of therapy.

5. Summary

We have reviewed the state of knowledge of CAH 150 years after the initial description and highlighted some recent advances in the field. Based on this review, we propose a research agenda and related questions for improved understanding and management of CAH (Box 1).

1. The mild phenotype

What would be the phenotype of a patient with nonclassic 17OHD? How many cases of nonclassic 11OHD are we missing? What is the minimum enzyme activity that distinguishes unaffected and nonclassic CAH patients?

2. Modifier genes

How can siblings with the same CAH genotype show very different phenotypes and disease control? What genes control drug metabolism, response to androgens, and peripheral metabolism of C_{19}-adrenal products? Why does salt wasting lessen in many but not all adults with classic 21OHD? Why do not all women with nonclassic 21OHD suffer from oligomenorrhea and subfertility?

3. Biomarkers for diagnosis and treatment

Can a panel of adrenal-derived 21-deoxysteroids be used to diagnose nonclassic 21OHD without cosyntropin stimulation and to eliminate false-positive newborn screens for classic 21OHD? Can similar panels be developed for 11OHD, 17OHD, POR, and 3βHSD2 deficiencies? What are the best steroids to use to monitor and titrate treatment?

4. Better treatments

What are the optimal glucocorticoid regimens? How do we position hydrocortisone as continuous subcutaneous infusion or modified-release oral preparations in treatment algorithms? Can we eliminate Cushingoid side effects and maintain control of androgen excess with the addition of abiraterone acetate, NBI77860, or other novel therapeutics to physiologic replacement doses of hydrocortisone?

5. Genetic diagnosis

Can cff-DNA in the maternal circulation be used to diagnose CAH and to determine sex chromosome complement for fetuses at risk for having CAH before 8 weeks' gestation? What is the value of whole-exome sequencing in children with suspected CAH?

This incomplete list represents a substantial amount of work. To answer these questions and accomplish these goals will take research funding, collaboration among and creativity from investigators, participation of patients and their families, and partnerships with the pharmaceutical industry. With advances in technology, biochemistry, and genetics, the time is right to make major advances in CAH, which will have important implications for other related and often more common diseases. These patients need better options today, and we cannot take another 150 years to bring these advances to fruition.

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Box 1. Areas of future research in congenital adrenal hyperplasia (CAH)

Research agenda

- *Diagnosis*
  - Biomarker panels for improved diagnosis of all nonclassic CAH forms
  - Early prenatal genetic diagnosis
- *Treatment*
  - Characterization of biomarkers for treatment monitoring and titration
  - Improved treatment modalities, to allow suppression of androgen excess while avoiding supraphysiologic doses of glucocorticoids.
- Elucidation of modifier genes/epigenetic contributors to phenotypes

Highlights

- Better steroid biomarkes might improve diagnosis and management of CAH
- Improved treatments might allow good control of CAH with low glucocorticoid doses
- The spectrum of mild or nonclassic CAH is known for most enzyme defects
- Important modifier genes for CAH remain to be discovered

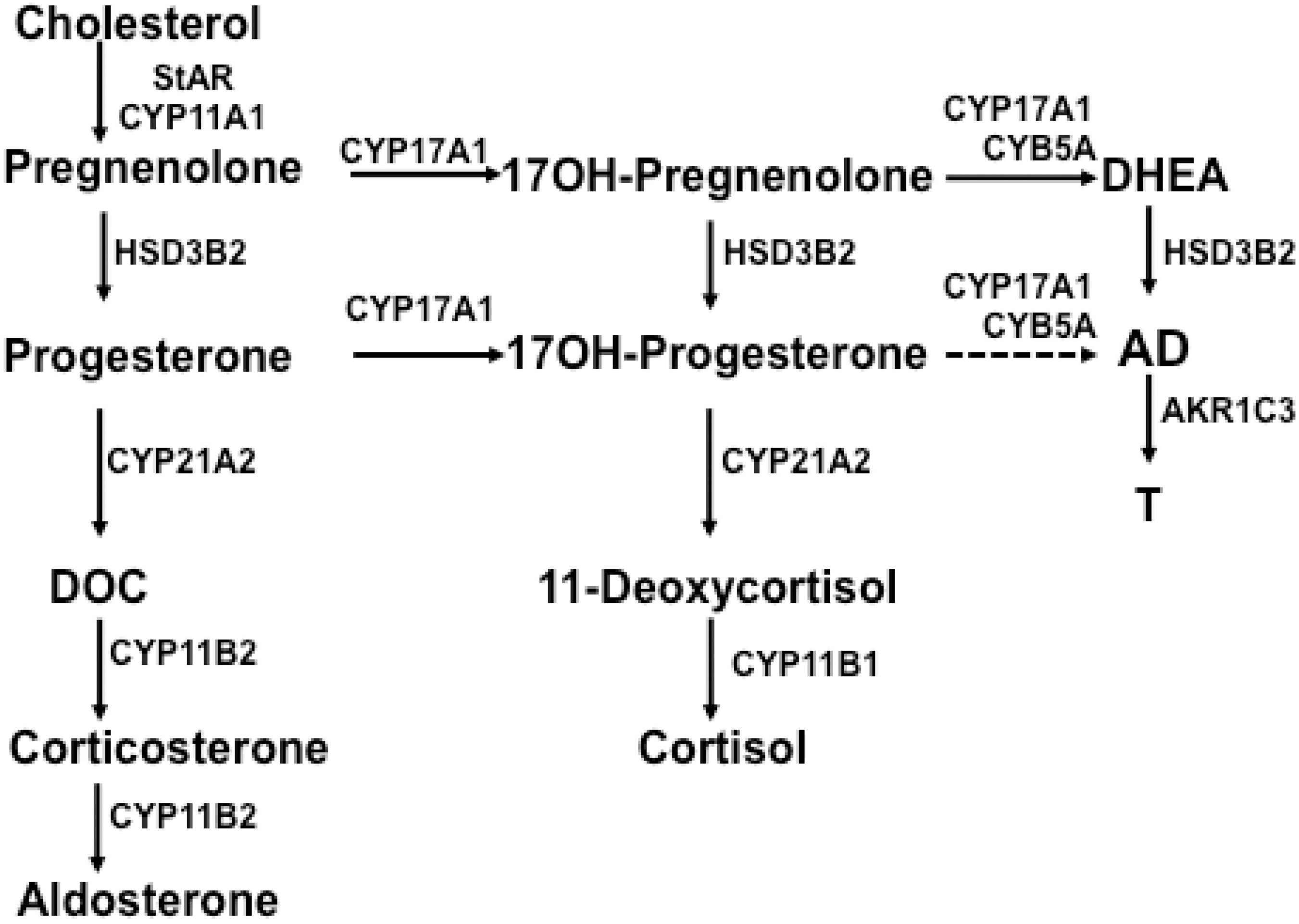

Figure 1.

Pathways of adrenal steroid hormone synthesis. StAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 cholesterol side-chain cleavage; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYB5A, cytochrome b_5; CYP21A2, 21-hydroxylase; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; DOC, 11-deoxycorticosterone; AD, androstenedione; T, testosterone.

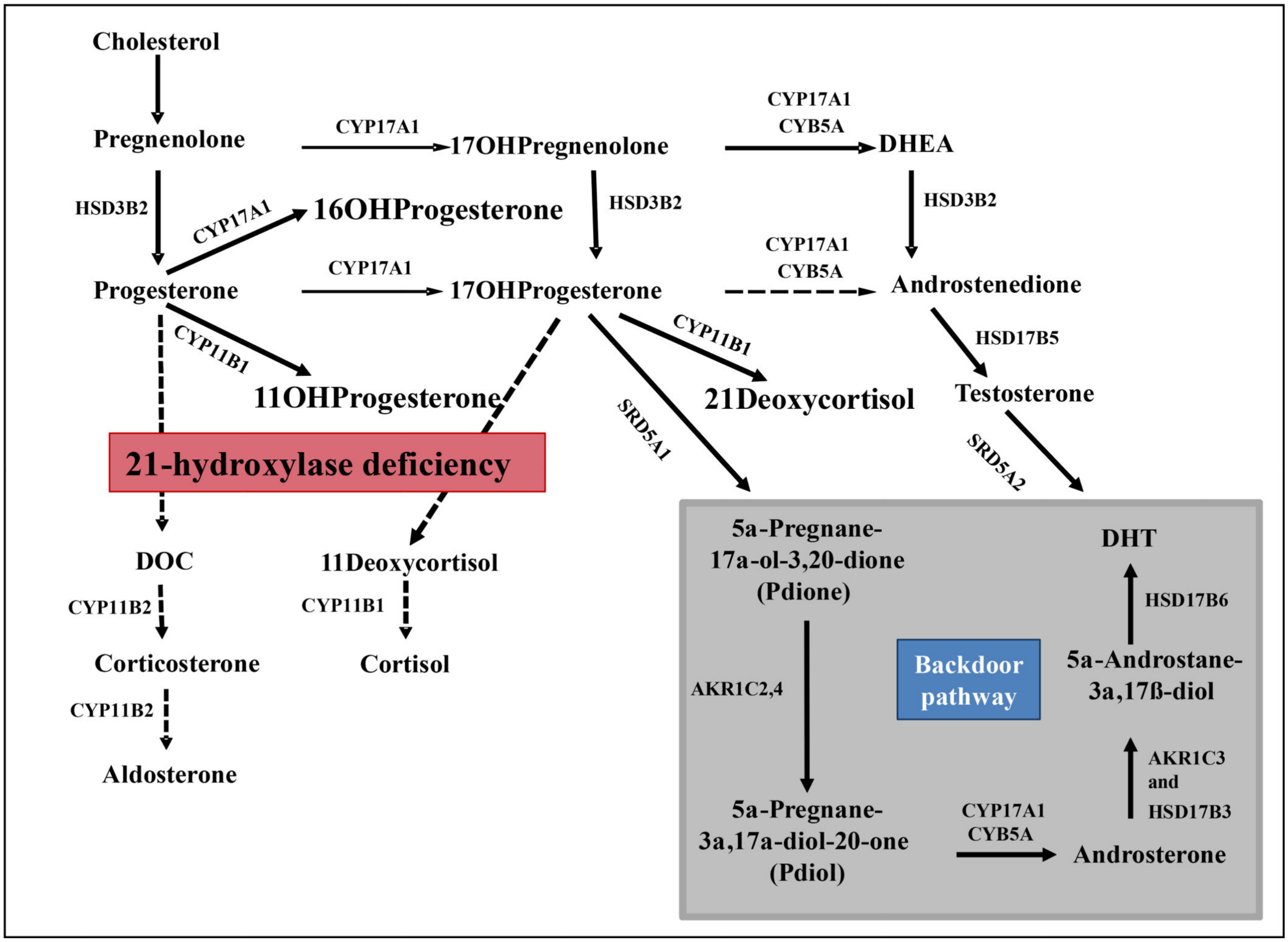

Figure 2.

Pathways of steroid hormone synthesis in 21-hydroxylase deficiency. HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYB5A, cytochrome b_5; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; DOC, 11-deoxycorticosterone; DHT, dehydrotestosterone; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; AKR1C2,4, aldo-keto reductase types 1C2 and 1C4; HSD17B6, 17β-hydroxysteroid dehydrogenase type 6 (an oxidative 3α-HSD); SRD5A1 and SRD5A2, 5α-reductase, types 1 and / 2, respectively.

Table 1

Forms of congenital adrenal hyperplasia

Defective enzyme	Gene/Chromosome	Incidence & Populations	Clinical features	Biomarkers
21-hydroxylase (P450c21)	*CYP21A2*/6p21.3	Classic 1:16,000 Nonclassic <1:1,000 More frequent in Ashkenazi Jews, Mediterraneans, Hispanics, and Yupik Eskimos.	Adrenal insufficiency in classic forms. Variable degrees of virilization.	17OH-progesterone, AD, T
11β-hydroxylase (P450c11β)	*CYP11B1*/8q24.3	1:100,000 in Caucasians; 1:7,000 in Moroccan Jews	Hypertension in most patients; hypokalemia; virilization	DOC, 11-deoxycortisol, AD, T
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2/1p13.1*	Rare	Volume depletion, hyponatremia, and hyperkalemia. 46,XX: virilization 46,XY: undervirilization	Pregnenolone, 17OH-pregnenolone, DHEA, DHEAS
17-hydroxylase/17,20-lyase (P450c17)	*CYP17A1*/10q21-q22	1:50,000 worldwide; More common in Brazil and Asia	Hypertension, hypokalemia, and hypogonadism; 46,XX: primary amenorrhea and absence of secondary sexual characteristics. 46,XY: undervirilization, abdominal testes.	Progesterone, DOC, corticosterone; LH & FSH
Steroidogenic acute regulatory protein (StAR)	*STAR*/8p11.2	Rare More frequent in Japanese, Palestinians, Koreans	Adrenal insufficiency; enlarged, lipid-laden adrenal glands. Female phenotype of external genitalia in both sexes	All steroids decreased
Cholesterol side-chain cleavage enzyme (P450scc)	*CYP11A1*/15q23–q24	Rare	Adrenal insufficiency; adrenal glands may appear absent.	All steroids decreased
P450-oxidoreductase deficiency (POR)	*POR*/7q11.2	Rare More common in Japan and Korea	Volume depletion, skeletal malformations (Antley-Bixler); maternal virilization. 46,XX: mild-to-moderate virilization. 46,XY: undervirilization	Highly variable profiles, multiple partial defects.

CYP11B1, 11β-hydroxylase; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; POR, P450-oxidoreductase deficiency; DOC, 11-deoxycorticosterone; AD, androstenedione; T, testosterone; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; LH, luteinizing hormone; FSH, follicle-stimulating hormone.