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Review

Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic

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ABSTRACT

Steroid 17-hydroxylase 17,20-lyase (cytochrome P450c17, P450 17A1, CYP17A1) catalyzes two major reactions: steroid 17-hydroxylation followed by the 17,20-lyase reactions. The most severe mutations in the cognate *CYP17A1* gene abrogate all activities and cause combined 17-hydroxylase/17,20-lyase deficiency (17OHD), a biochemical phenotype that is replicated by treatment with the potent CYP17A1 inhibitor abiraterone acetate. The adrenals of patients with 17OHD synthesize 11-deoxycorticosterone (DOC) and corticosterone but no 19-carbon steroids, similar to the rodent adrenal, and DOC causes hypertension and hypokalemia. Loss of 17,20-lyase activity precludes sex steroid synthesis and leads to sexual infantilism. Rare missense *CYP17A1* mutations minimally disrupt 17-hydroxylase activity but cause isolated 17,20-lyase deficiency (ILD), Mutations in the *POR* gene encoding the required cofactor protein cytochrome P450-oxidoreductase causes a spectrum of disease from ILD to 17OHD combined with 21-hydroxylase and aromatase deficiencies, sometimes including skeletal malformations. Mutations in the *CYB5A* gene encoding a second cofactor protein cytochrome b_5 also selectively disrupt 17,20-lyase activity and cause the purest form of ILD. The clinical manifestations of these conditions are best understood in the context of the biochemistry of CYP17A1.

Contents

1. Physiology, genetics, and biochemistry of CYP17A1

1.1. Physiology

All vertebrates that exhibit sexual dimorphism and reproduction require the 17,20-lyase activity of CYP17A1 to synthesize

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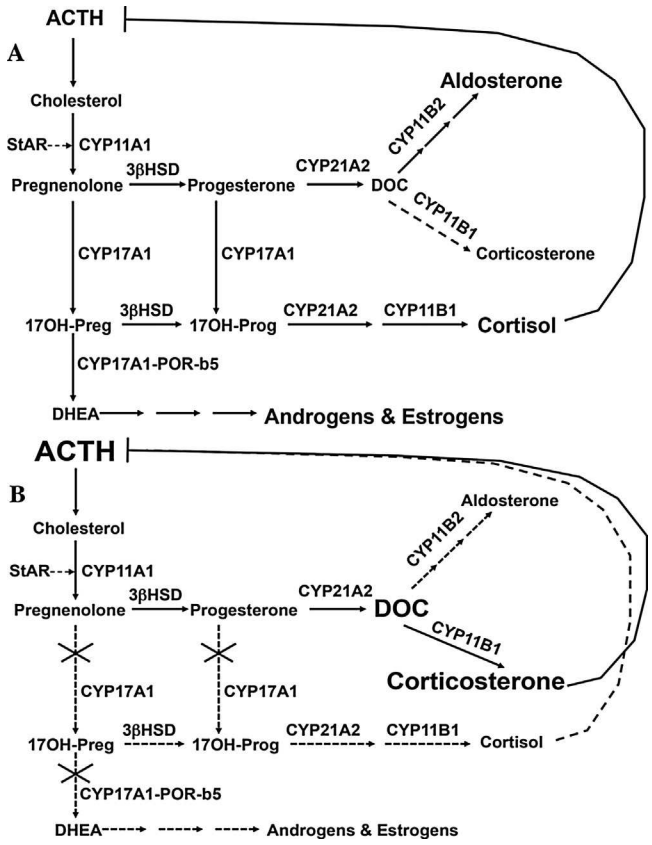

Fig. 1. Major pathways of human adrenal steroid biosynthesis. Panel (A) shows the pathways in the normal adrenal, and panel (B) shows altered pathways in 17OHD. Dashed arrows show minor or reduced pathways, and size of text indicates relative abundance for cortisol, aldosterone, androgens and estrogens, corticosterone, and DOC (11-deoxycorticosterone).

19-carbon androgens and subsequently 18-carbon estrogens (Fig. 1A). *CYP17A1* genes are expressed in the gonads of all these organisms for this purpose. Zebrafish [1] and trout [2] contain 2 *CYP17A1* genes, which are both expressed under different regulation, and 1 enzyme has only 17-hydroxylase activity while the other also has 17,20-lyase activity. Based on its location in the steroidogenic pathways, CYP17A1 is the exclusive gateway to sex steroid production. As will be explored below, the substrates for the 17,20-lyase reaction are 17-hydroxysteroids—the products of the 17-hydroxylase reaction, which CYP17A1 also catalyzes. In fact, the 17-hydroxylase activity is only required in animal physiology to generate intermediates for subsequent conversion to androgens. For example, rodents express CYP17A1 only in the gonads but not in the adrenal glands. Rats and mice produce corticosterone as their dominant glucocorticoid rather than cortisol for this reason (Fig. 1B). Thus, the 17-hydroxylase reaction would be completely dispensable if CYP17A1 could generate 17-ketosteroids directly from 17-deoxypregnanes such as pregnenolone.

Nevertheless, the balance of enzyme activities and substrate preferences in the adrenal varies amongst species, as do sensitivities of their nuclear hormone receptors for various steroids, plasma steroid binding capacities, and pathways of steroid catabolism. As a result, human beings need adrenal 17-hydroxylase activity to produce cortisol and to maintain glucocorticoid and mineralocorticoid homeostasis. Based on this analysis, complete deficiency of CYP17A1, like all forms of congenital adrenal hyperplasia, features both consequences of hormone deficiency—what is lacking after the block—and hormone excess—what accumulates upstream of the block. The hormone deficiency is really only the gonadal component, lack of androgens and estrogens, which causes sexual infantilism and pubertal failure. The absence of 17,20-lyase activity in the adrenal results in deficiency of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), which prevents adrenarche and the development of pubic and axillary hair—not a significant matter in health and bodily function.

The lack of adrenal 17-hydroxylase activity, however, forces steroidogenesis to corticosterone rather than cortisol via 11-deoxycorticosterone (DOC), which in human beings is normally a very minor adrenal product. DOC, however, is a mineralocorticoid, which is slightly less potent than aldosterone. In the face of complete 17-hydroxylase deficiency (17OHD), nascent pregnenolone is converted to progesterone and then to DOC and corticosterone. Circulating corticosterone rises from typical concentrations of <400 ng/dL (~10 nM) to nearly 40,000 ng/dL (~1 μM), which adequately substitutes for cortisol for supplying glucocorticoid activity, even if >90% is protein-bound (Table 1). In parallel, circulating DOC concentrations rise from <20 ng/dL (~0.6 nM) to >300 ng/dL (~10 nM), which saturates the mineralocorticoid receptor under most circumstances. Consequently, adrenal 17OHD does not really result in glucocorticoid deficiency despite the lack of cortisol synthesis, but the important physiologic disturbance is low-renin hypertension from DOC excess.

1.2. Genetics

The human *CYP17A1* gene is located on chromosome 10q24.3 [3], spans 6.6 kb, and contains eight exons [4]. An identical 2.1 kb mRNA is transcribed from this gene in the both the adrenals and gonads [5]. From the 1.6 kb coding region, a 57 kDa polypeptide is translated. The protein resides in the smooth endoplasmic reticulum with the flavoprotein cofactor P450-oxidoreductase (POR). The enzyme system of CYP17A1 and POR catalyzes both the 17-hydroxylase and 17,20-lyase activities [6]. In cells with high 17,20-lyase activity, cytochrome b_5 (b5) is also present with CYP17A1 and POR in the endoplasmic reticulum [7]. Collectively, POR and b5 are known as "redox partners," since both are electron-transfer proteins. The importance of b5 in activating maximal 17,20-lyase activity will be discussed later.

Over 100 mutations in the *CYP17A1* gene have been associated with combined 17-hydroxylase/17,20-lyase deficiency (OMIM 202110), including point mutations, small insertions or deletions, splice site alterations, and rarely large deletions (Fig. 2A). Although these mutations can be found throughout the gene, many occur near the C-terminus, emphasizing the importance of even the last

Table 1
Steroid changes in combined 17-hydroxylase/17,20-lyase deficiency.

Steroid	Normal adult range	17OHD
Progesterone (ng/mL, follicular phase)	<0.2	2–40
17-Hydroxyprogesterone (ng/dL)	50–200	10–100
11-Deoxycorticosterone (ng/dL)	<20	100–1000
Corticosterone (ng/dL)	100–800	4000–40,000
11-Deoxycortisol (ng/dL)	10–160	<5
Cortisol (μg/dL)	2–25	<2
DHEAS (μg/dL, young adult)	100–400	<10
Aldosterone (ng/dL)	2–10	<5
Androstenedione (ng/dL)	25–250	<50
Testosterone (ng/dL)		
46,XX	10–50	<20
46,XY young adult	400–900	<20
Estradiol (pg/mL)		
46,XX follicular phase	40–100	<20
46,XY	10–40	<20

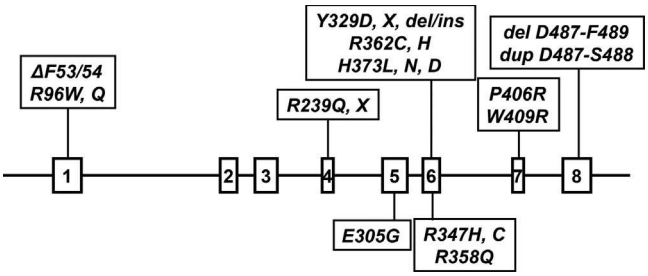

Fig. 2. Cartoon of *CYP17A1* gene showing the location of common mutations and mutations causing isolated 17,20-lyase deficiency. Exons are shown as numbered rectangles connected by introns as solid horizontal line and are approximately drawn to scale. Mutations found in isolated 17,20-lyase deficiency are shown below the gene cartoon.

14 amino acids for enzyme activity. Splice site mutations can lead to "exon skipping" and truncated, inactive protein [8,9]. Some frameshift mutations introduce premature stop codons, which also yield truncated proteins. The most commonly mutated residues include Y329 (to D, X, or frameshift TAC → AA with 418X), R362 (to C or H), and H373 (to L, N, or D) in exon 6; W406 (to R) in exon 7; and deletion of D487-S488-F489 or a CATC duplication within D487-S488 in exon 8. For some patients with a clinical and hormonal diagnosis of 17OHD, no *CYP17A1* mutations have been identified [10]. Cases of incomplete 17-hydroxylase deficiency combined with partial 21-hydroxylase deficiency can result from mutations in POR, but the biochemical and phenotypic spectrum of POR deficiency can be quite variable [11,12].

In Brazil, CYP17A1 deficiency appears to be the second most common cause of congenital adrenal hyperplasia, due to founder mutations R362C and W406R [13]. In a large series from China, the aforementioned Y329 frameshift and D487-F489 deletions accounted for >80% of the affected alleles in 26 affected individuals [14]. These positions appear to be mutational "hot spots," as the same mutations have been identified in other ethnic groups in Asia [15] and elsewhere. A duplication of four nucleotides at amino acid 478, which induces a frameshift and premature stop codon, has been found in Dutch Frieslanders and in Canadian Mennonites [16], and a phenylalanine 53 deletion has been identified in Japan and elsewhere [17].

A special case of CYP17A1 dysfunction is isolated 17,20-lyase deficiency (ILD, Fig. 2B). In these rare cases, missense mutations preferentially impair 17,20-lyase activity and leave 17-hydroxylase activity largely unaffected. Mutations R347H or C and R358Q map to the enzyme surface, and these mutations impair interactions of CYP17A1 with POR and more importantly with b5 [18–21], thus explaining a selective deficiency of 17,20-lyase activity. Mutation E305G is located in the active site and also preferentially impairs the 17,20-lyase activity [22], yet homozygous patients bearing this mutation show some biochemical but not clinical evidence of 17-hydroxylase impairment, with increased excretion of DOC and corticosterone metabolites [23]. POR mutation G539R causes ILD, which is clinically and biochemically a phenocopy of ILD caused by CYP17A1 mutations [24,25].

1.3. Biochemistry

Like all cytochrome P450 enzymes, CYP17A1 follows a catalytic cycle, including 2 one-electron transfers from reduced nicotinamide adenine dinucleotide phosphate (NADPH) via POR, binding of substrate and oxygen, formation of the reactive heme-iron complex with oxygen in concert with O—O bond scission and water release, and finally substrate oxidation [26]. The co-existence of two major activities in one enzyme was first demonstrated with the co-purification of 17-hydroxylase and 17,20-lyase activities from neonatal porcine testes [27]. Purified CYP17A1 disproportionately loses 17,20-lyase activity during purification as b5 is removed from the system, and addition of a stoichiometric amount of b5 restores the lost 17,20-lyase activity [28–30]. The effect of b5 is not subtle—a 10-fold increase in 17,20-lyase activity for 17-hydroxypregnenolone (17 Preg) and 17-hydroxyprogesterone (17OHP) substrates [31] or a 3-fold stimulation with 5α-pregnane-3α,17α-diol-20-one, the best 17,20-lyase substrate for human CYP17A1 [32]. The importance of the b5 effect is illustrated in patients with mutations in the *CYB5A* gene, which causes the purest form of ILD [33,34].

CYP17A1 from various species all appear to 17-hydroxylate both pregnenolone and progesterone with comparable efficiencies, and this property is true for the human enzyme [30,31]. Human CYP17A1 also 16α-hydroxylates 20–25% of progesterone but not pregnenolone [35], and the presence of A rather than L at residue 105 allow for this high proportion of 16α-hydroxylation [36]. With progesterone substrate, human CYP17A1 also affords <1% DOC—the 21-hydroxylation product, and this fraction can be increased by deuterium incorporation at C-17 [37]. The X-ray crystal structures of modified wild-type human CYP17A1 with bound inhibitors [38] and mutation A105L with bound substrates [39] help to explain the

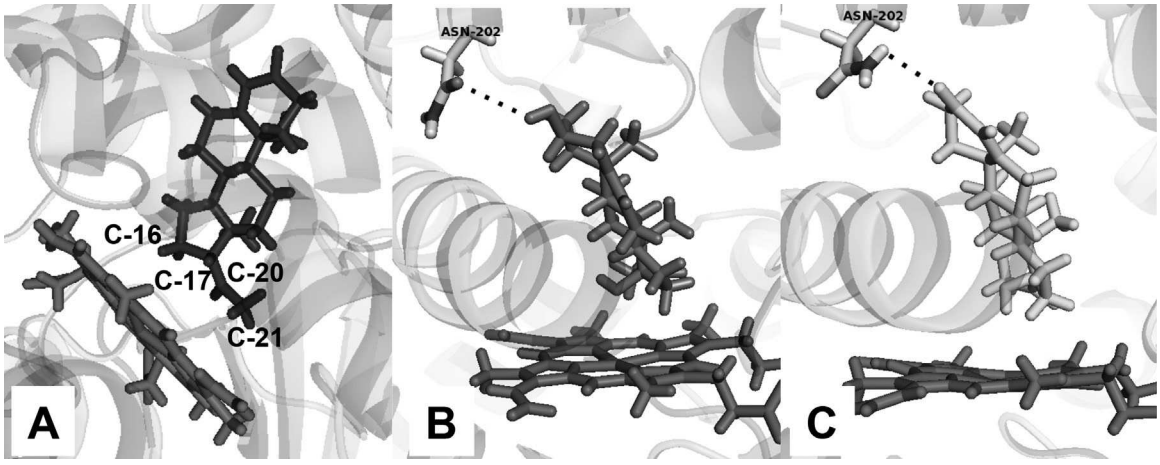

Fig. 3. Steroid-binding pocket in human CYP17A1. Images demonstrate proximity of hydrogen atoms at C-16, C-17, and C-21 of progesterone to heme ring (A) and hydrogen bonding (arrows) of A-ring oxygen to side-chain of N202 in 17-hydroxypregnenolone (B) or 17-hydroxyprogesterone (C). Images were generated from the X-ray crystal structures of CYP17A1 mutation A105L with bound steroids (pdbid numbers 4NKX, 4NKY, 4NKZ) with program PyMol.

diverse chemistry in this enzyme. The steroid rests against the I-helix perpendicular to the heme ring with the steroid D-ring closest to the heme iron and the A-ring pointing away to the center of the enzyme (Fig. 3A). In this orientation, the hydrogen atoms on carbon atoms 16, 17, and 21 are all within the minimum distance to react with the iron-oxygen species, and the order of reactivity parallels the stability of carbon-centered radicals formed during catalysis [26,40].

In contrast to the similar activities with 17-deoxypregnanes for the 17-hydroxylase reaction, CYP17A1 from various species often show strong preferences among 17-hydroxysteroid substrates for the 17,20-lyase reaction. Human CYP17A1 catalyzes the 17,20-lyase reaction approximately 50-times more efficiently with 17Preg substrate than with 17OHP, and b5 markedly stimulates both reactions [30,31]. As a consequence, the human adrenal zona reticularis produces large amounts of DHEA, which is sulfated and circulates as DHEAS [41]. In the X-ray crystal structures of CYP17A1 mutation A105L with 17Preg (Fig. 3B) or 17OHP (Fig. 3C), the A-ring hydroxyl- or keto-group form a hydrogen bond with the carbonyl oxygen or amide hydrogen of N202, respectively [39]. Despite slightly different positioning of the steroid D-rings, these structures alone do not explain the difference in reactivity [26].

2. Clinical presentation and diagnosis

2.1. Clinical presentation

Severe mutations of CYP17A1 cause complete 17OHD, which disrupts steroidogenesis in both the adrenals and the gonads. The production of both androgens and estrogens requires the 17,20-lyase activity of CYP17A1 and the availability of 17-hydroxysteroid substrates for this reaction, which are exclusive products of CYP17A1 as well. Thus, pubertal failure is one of the major features of 17OHD. In addition, individuals with both 46,XX and 46,XY karyotypes will have female external genitalia from absent testosterone (T) and dihydrotestosterone (DHT) synthesis in fetal life, but the 46,XY individuals will not have internal Müllerian structure, due to preservation of anti-Müllerian hormone from the testes. Occasionally, the 46,XY children are identified due to inguinal hernia or discrepancy between external (female) genitalia and chromosomal sex obtained from amniocentesis, performed for other reasons.

The second major feature of 17OHD derives from the adrenal enzyme deficiency. Unlike all other forms of congenital adrenal hyperplasia, infants are not glucocorticoid deficient, even though their cortisol production is low. In the absence of adrenal 17-hydroxylase activity, corticosterone accumulates and substitutes for cortisol, similar to the physiology of the rodent adrenal. Consequently, adrenal crisis is very rare in 17OHD, and children escape diagnosis until adolescence for this reason. Instead, the precursor DOC accumulates, but manifestations of mineralocorticoid excess tend not to occur in infancy because the newborn kidney is rather insensitive to mineralocorticoids. Gradually and typically in adolescence, DOC excess causes hypertension and hypokalemia. Thus, the most common presentation of 17OHD is an adolescent girl without secondary sexual characteristics or menses and low-renin hypertension [42,43]. The hypokalemia can be severe and cause muscle cramps or frank tetany, which can be the

Table 2
Differential diagnosis and distinguishing features.

Infant			
46,XX/45,X	17OHD	Turner	PORD
Turner stigmata	Absent	Present	Absent
Skeletal anomolies	Absent	Absent	±Present
Genitalia	Prader 1	Prader 1	Prader 1–4
Gonadotropins	High	High	High
17OHP	Low/Nl	Nl	High

Infant					
46,XY	17OHD	AIS/5αRD	PORD	17βHSD3D	Gon dys
Skeletal anomolies	Absent	Absent	±Present	Absent	Absent
Genitalia	Prader 1–3	Prader 1–2	Prader 2–4	Prader 1–3	Prader 1–2
17OHP	Low/Nl	Nl	High	Nl	Nl
Testosterone	Low	Nl male	Low	Low	Low
Androstenedione	Low	Nl male	Low	High	Low
Cortisol	Low	Nl	Low	Nl	Nl
DOC	High	Nl	Nl	Nl	Nl
Corticosterone	High	Nl	Nl or high	Nl	Nl

Adolescent and adult			
46,XX/45,X	17OHD	Turner/Gon dys	PORD
Blood pressure	High	Nl or high	Nl
Stature	Nl or tall	Short or Nl	Nl
Estradiol	Low	Low	Low
Cortisol	Low	Nl	Low
DOC	High	Nl	Nl

Adolescent and adult				
46,XY	17OHD	AIS	17βHSD3D/5αRD	Gon dys
Blood pressure	High	Nl	Nl	Nl
Pubertal virilization	Absent	Absent/partial	Present	Absent
Testosterone	Low	Nl male	Low/low Nl	Low
Cortisol	Low	Nl	Nl	Nl
DOC	High	Nl	Nl	Nl

Gonadal dysgenesis; gon dys, AIS; androgen insensitivity syndrome, 5αRD; 5α-reductase deficiency, 17βHSD3D; 17βHSD3 deficiency.

presenting symptom complex. In addition, like other forms of mineralocorticoid-mediated hypertension, the blood pressure is resistant to common antihypertensive agents yet responds well to mineralocorticoid-receptor antagonists (MRA) such as spironolactone.

In the differential diagnosis, 17OHD patients with 46,XX karyotypes resemble Turner syndrome with Müllerian structures and absent secondary sexual characteristics; however, the 17OHD patients lack the other Turner stigmata (lymphedema, wide carrying angle, cardiac defects) and are typically normal height or tall rather than short. The 17OHD patients with 46,XY karyotype somewhat resemble complete androgen insensitivity syndrome due to the blind vaginal pouch without Müllerian structures or body hair, but the 17OHD patients fail to feminize spontaneously and will respond to androgens if administered. Also on the differential diagnosis is P450-oxidoreductase deficiency (PORD), which itself has partial but variable deficiency of 17-hydroxylase and 17,20-lyase activities. Because of overlapping hormonal abnormalities in PORD and 17OHD, the two conditions can be difficult to distinguish in 46,XY individuals (Table 2). In contrast, PORD patients with 46,XX karyotypes often show inappropriate masculinization for complex biochemical reasons. Additional clues to PORD include elevated 17OHP and 21-deoxycortisol as in 21-hydroxylase deficiency, the presence of Antley-Bixler syndrome malformations in some but not all cases, and maternal virilization during pregnancy.

Unlike most other forms of congenital adrenal hyperplasia, a true nonclassic form of 17OHD has not been well defined—meaning normal cortisol production and prenatal sexual development but discernable genetic and biochemical abnormalities with subtle clinical manifestations. One could speculate that such patients might have what would appear to be low-renin "essential" hypertension with low aldosterone, but because DOC is rarely measured in clinical practice, a genetic condition would not be suspected. The closest case so far described is a child with mild undervirilization, normal blood pressure, and biochemical evidence of partial 17OHD [44]. This child is a compound heterozygote for a frameshift mutation in R36, creating a stop codon at residue 107, and W121R, which shows 60% 17-hydroxylase and 16% 17,20-lyase activity of the wild-type enzyme. Indeed, the rs1004467 polymorphism in the *CYP17A1* gene has been identified as a susceptibility allele for hypertension in several studies [45,46], but this single-nucleotide polymorphism does not change the coding region of the enzyme. Females with mild 17OHD might have irregular menses and subfertility, while affected males might have low-normal testosterone with slightly elevated gonadotropins and possibly oligospermia.

Additional manifestations of 17OHD include ovarian cysts and cyst rupture in 46,XX patients [47,48]. The mechanism of cyst formation is thought to be chronically elevated gonadotropins without an estrogen-triggered ovulatory surge. Occasionally, 46,XX patients with 17OHD have spontaneous but irregular menses [49,50]. At this time, there are no published examples conclusively documenting a successful pregnancy in which either partner has 17OHD. Cases of 46,XX women with 17OHD have been described in whom embryos were obtained after adrenal-derived progesterone suppression with dexamethasone prior to superovulation with gonadotropins, oocyte retrieval, and in vitro fertilization, but these embryos have not afforded live births [51].

Boys with ILD are usually ascertained at birth because of impaired virilization [18,22,52], and girls with this condition have been identified as siblings of affected boys [52] or during evaluation of primary amenorrhea without hypertension [53]. The boys show varying degrees of poor genital development with hypospadias, bifid scrotum, and micropenis. Both girls and boys with this condition do not progress normally through puberty and are likewise infertile.

2.2. Diagnosis

The two scenarios most commonly encountered in which the diagnosis of 17OHD is entertained include the infant with 46,XY karyotype and female or ambiguous genitalia and inguinal or abdominal testes, or the adolescent girl with primary amenorrhea and absent secondary sexual characteristics with hypertension and hypokalemia [42]. In the first case, the infant will have had the karyotype and initial laboratory findings of low T with high gonadotropins. At that point, androgen insensitivity and 5α-reductase deficiency are essentially excluded, so the differential diagnosis primarily includes various forms of gonadal dysgenesis and 17β-hydroxysteroid dehydrogenase type 3 deficiency. Cosyntropin stimulation testing reveals the adrenal steroidogenic defect: low cortisol, DHEA, and 17OHP but high DOC and corticosterone [13,54]. As in all cases of enzyme deficiency, the most informative tests are the high analytes above the block, particularly corticosterone. Progesterone is also above the block and is high in 17OHD [55] and even higher in PORD [56,57], but low 17OHP and very high DOC distinguishes 17OHD from PORD [58]. Finally, the other hypertensive form of congential adrenal hyperplasia is 11-hydroxylase deficiency (11OHD), because DOC also accumulates, but 11-deoxycortisol is low in 17OHD and high in 11OHD. Androgens are also elevated in 11OHD but low in 17OHD [13,59].

For the adolescent girls with primary amenorrhea, the initial evaluation will suggest a form of gonadal dysgenesis: high gonadotropins, low T, and low estradiol (E2), regardless of karyotype. The 46,XY cases will also lack a uterus and might have palpable testes in the inguinal regions. While the focus in these cases is on the gonads and reproductive development, the critical step in making the correct diagnosis is the consideration of a simultaneous defect in adrenal steroidogenesis, which is hinted in the majority of cases from the presence hypertension and/or hypokalemia. Steroid analysis, basal and after cosyntropin stimulation, will reveal the biosynthesis defect as described for infants.

The diagnosis of ILD is primarily considered for newborn boys with undervirilization. The presumptive diagnosis of gonadal dysgenesis will be consistent with initial laboratory tests, which show low AD and T and often high gonadotropins. Among the distinguishing laboratory features is the elevated 17OHP/AD ratio at baseline or with hCG stimulation, which is typically >50 in affected cases [18]. A second clue to the diagnosis in the neonate is a low DHEAS, which is normally >100 μg/dL but falls sharply after birth [41]. The low DHEAS indicates both an adrenal and gonadal defect and focuses the differential diagnosis on enzymes common to both glands, including CYP17A1. For girls, ILD is a very rare cause of pubertal failure but without hypertension as in 17OHD [53].

2.3. Abiraterone acetate and pharmacologic induction of 17OHD

The prostate gland requires androgens for its formation and growth, and prostate cancer likewise demonstrates androgen dependence in most cases. For this reason, surgical or medical castration has been used for decades to treat this disease, at least in the initial stages. Currently, the standard of care in metastatic disease is testicular suppression with long-acting gonadotropin-releasing hormone agonists or antagonists, which often induces remission or stable disease for months to years [60]. When the disease progresses despite therapy, the condition is called castration-resistant prostate cancer (CRPC), and evidence from the past decade has shown that traces of residual androgens are primarily responsible for disease progression [61,62]. Because

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