Fertility in patients with genetic deficiencies of cytochrome P450c17 (CYP17A1): combined 17-hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency

Courtney A. Marsh, M.D., M.P.H.,[a] and Richard J. Auchus, M.D., Ph.D.[b]

[a] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Kansas, KU Medical Center Office, Kansas City, Kansas; and [b] Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

CYP17A1 catalyzes the 17-hydroxylase and 17,20-lyase reactions, regulating the steroid hormones produced by the adrenal glands and gonads. Mutations that compromise all CYP17A1 activities are extremely rare and cause combined 17-hydroxylase/17,20-lyase deficiency. Clinically, combined 17-hydroxylase/17,20-lyase deficiency presents with hypertension, hypokalemia, primary amenorrhea, and sexual infantilism. A few mutations selectively impair 17,20-lyase activity, and some mutations in cofactor proteins cytochrome P450-oxidoreductase and cytochrome b_5 also selectively disrupt 17,20-lyase activity. The defect in sex steroid synthesis impairs fertility in both male and female patients when the deficiency is severe. This paper reviews the genetics, steroidogenesis, and fertility impairments associated with these disorders. (Fertil Steril® 2014;101:317–22. ©2014 by American Society for Reproductive Medicine.)

Key Words: Hypertension, androgen, mineralocorticoid, 17-hydroxylase/17,20-lyase, sexual infantilism, 46,XY DSD, infertility, primary amenorrhea

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/marshc-fertility-17-hydroxylase-17-20-lyase-hypertension/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

CYP17A1 GENE DEFECT

The human *CYP17A1* gene is located on chromosome 10q24.3 (1) and spans 6.6 kb, which contain eight exons (2) and 1.6 kb of coding region. From this gene, the same 2.1-kb mRNA species is transcribed in both the adrenals and gonads (3), which yields a 57-kDa microsomal cytochrome P450c17 enzyme (CYP17A1). The CYP17A1 enzyme catalyzes both steroid 17-hydroxylase and 17,20-lyase activities (4), and both activities require one equivalent of molecular oxygen and two electrons from nicotinamide adenine dinucleotide phosphate (reduced form, NADPH). The electron transfer flavoprotein, cytochrome P450 oxidoreductase (POR), serves as a conduit for the electron transfer from NADPH to CYP17A1, but other flavoproteins can substitute for POR, at least for the 17-hydroxylase activity (5). The 17,20-lyase activity is particularly vulnerable to the abundance and structure of the electron transfer complex (6). In addition, optimal 17,20-lyase reaction requires the cofactor protein cytochrome b_5 (b5); b5 stimulates the maximal rate of the reaction in the steady state over 10-fold (7–10).

Nearly 100 disease-causing mutations 17-hydroxylase/17,20-lyase deficiency (17OHD, OMIM 202110) have been described. All forms of CYP17A1 deficiency are extremely rare, and in most populations without founder mutations, 17OHD accounts for $<1\%$ of all cases of congenital adrenal hyperplasia (CAH). Although 17OHD patients are found worldwide, the disease is

Received October 1, 2013; revised November 2, 2013; accepted November 7, 2013.
C.A.M. has nothing to disclose. R.J.A. has nothing to disclose.
Reprint requests: Richard J. Auchus, M.D., Ph.D., University of Michigan, MEND/Internal Medicine, Rm 5560A MSRBII, 1150 W. Medical Center Drive, Ann Arbor, MI 48105 (E-mail: rauchus@med.umich.edu).

Fertility and Sterility® Vol. 101, No. 2, February 2014 0015-0282/$36.00
Copyright © 2014 Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine
http://dx.doi.org/10.1016/j.fertnstert.2013.11.011

particularly abundant in Brazil owing to two founder mutations, R362C and W406R. Other mutations are found repeatedly, such as Y329 mutations and a deletion of residues 487–489, particularly in Asia. Mutations are found throughout the gene, with the largest number in the C-terminus, up to the last 14 amino acids. The majority of these changes are missense or nonsense single base pair substitutions, and residues prone to mutation of one or more base change include R96, R239, Y329, R362, H373, R347, R416, R440, D487, and R496. A few small deletions and duplications have been described, and large deletions account for a very few cases. In some cases, no *CYP17A1* mutations have been located, despite clinical and hormonal evidence for 17-hydroxylase deficiency (11). Table 1 lists some of the more common *CYP17A1* mutations causing combined 17OHD.

DEFECTS IN STEROIDOGENESIS

CYP17A1 is the major qualitative regulator of steroidogenesis (12), meaning that CYP17A1 activities determine which steroid products derive from a given cell. CYP17A1 is absent in the zona glomerulosa of the adrenal and the corpora lutea of the ovary, and its expression in the placenta is low. In the adrenal zona glomerulosa, the enzyme steroid 21-hydroxylase (cytochrome P450c21, CYP21A2) converts P to 11-deoxycorticosterone (DOC). Ordinarily, the coexpression of aldosterone synthase (cytochrome P450c11AS, CYP11B2) completes the synthesis of aldosterone from DOC via three sequential oxygenations, one at C-11 and two at C-18. In the placenta and corpora lutea, the steroid hydroxylases are essentially absent, and steroidogenesis stops at P. In 17OHD and isolated 17,20-lyase deficiency, steroidogenesis mirrors the normal steroid biosynthesis in these tissues, and the physiology derives from androgen deficiency and varying degrees of mineralocorticoid excess (Fig. 1).

TABLE 1

Selected recurring mutations in *CYP17A1* causing combined 17OHD.

Mutation	Activity	Exon
delF53/54 (3 bp)	37%	1
R96W, Q	5%–25%, Nil	1
dup Ile112 (3 bp)	Nil	2
R239X	ND	4
Y329X	Nil	6
del/sub Y329K (TAC→AA, 418X)	Nil	6
ins A Y329X (TAC→TAA)	ND	6
R358X	Nil	6
R362C, H	Nil, ND	6
H373L, N, D	Nil	6
W406R	Nil	7
P409R	Nil	7
R416C	8%	8
R416H	Nil	8
P428L	<5%	8
R440H, C	Nil	8
R449C	ND	8
Q461X	Nil	8
dup D487-S488 (4 bp)	Nil	8
del D487-F489 (9 bp)	Nil	8
R496C, H	<10%, 33%–38%	8

Note: ND = not determined.

Marsh. Fertility and 17-hydroxylase/17,20-lyase deficiencies. Fertil Steril 2014.

Complete 17OHD

With complete deficiency of CYP17A1 (complete 17OHD), the hormonal abnormalities are summarized as androgen and estrogen deficiency with mineralocorticoid excess (13). In the adrenals, the block in cortisol biosynthesis is compensated physiologically by augmented ACTH-driven corticosterone excess (Fig. 1), which substitutes for cortisol as a glucocorticoid and prevents clinical adrenal insufficiency. The increased flux of steroids in the 17-deoxysteroid pathway, however, allows the cortisol precursor DOC to accumulate to a concentration one to two orders of magnitude above normal or higher. DOC is slightly less potent than aldosterone as a ligand for the mineralocorticoid receptor (MR), and DOC concentrations of 100 ng/dL (3 nM) activate MR and cause the hypertension and hypokalemia characteristic of 17OHD. Corticosterone is also a good MR ligand, and corticosterone excess also contributes to the hypertension of 17OHD.

The DOC and corticosterone excess in 17OHD expands plasma volume and suppresses plasma renin activity. As a result, CYP11B2 expression and aldosterone production are also low or absent in untreated patients with 17OHD (14, 15). Additional steroid abnormalities in 17OHD include elevated 18-hydroxysteroids, particularly 18-hydroxyDOC and 18-hydroxycorticosterone (16, 17) (Fig. 1). These 18-oxygenated steroids derive from the zona fasciculata of the adrenal cortex, where expression of steroid 11β-hydroxylase (cytochrome P450c11β, CYP11B1) is high. CYP11B1 has 18-hydroxylase but not 18-oxidase activity, yielding 18-hydroxysteroids but not 18-oxo-steroids such as aldosterone. In addition, other atypical metabolites of these cortisol precursors are found in 17OHD patients, including 19-norDOC. P also accumulates above the block at 17-hydroxylase, and high P is found in 17OHD (18) as well as in other forms of CAH except lipoid CAH, particularly in POR deficiency (19, 20).

Impaired androgen production derives both from deficient generation of the 17-hydroxysteroid substrates for the 17,20-lyase reaction and from poor or absent 17,20-lyase activity itself. Estrogens derive from aromatization of androgens via the aromatase enzyme (cytochrome P450aro, CYP19A1). Consequently, neither androgens nor estrogens are produced from the gonads in complete 17OHD.

Based on the physiology and biochemistry described above, all individuals with complete 17OHD are born with sexual infantilism and fail to develop secondary sexual characteristics. Patients with 17OHD and 46,XX karyotypes have internal Müllerian structures with streak gonads. Patients with 17OHD and 46,XY karyotypes have a blind vaginal pouch owing to the absence of masculinization resulting from defective androgen production.

Partial 17OHD

For partial CYP17A1 deficiency to be identified, the defect must be sufficiently severe to cause clinical manifestations. Consequently, these patients are usually similar to complete

Download English Version:

https://daneshyari.com/en/article/6182155

Download Persian Version:

https://daneshyari.com/article/6182155

Daneshyari.com