Mini-Review

Congenital Adrenal Hyperplasia

Selma Feldman Witchel MD [1,*], Ricardo Azziz MD, MPH, MBA [2]

[1] Division of Pediatric Endocrinology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
[2] Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center; Department of Obstetrics and Gynecology, and Medicine, The David Geffen School of Medicine at UCLA, Los Angeles, California; and Office of the President, Medical College of Georgia, Augusta, Georgia, USA

A B S T R A C T

Congenital adrenal hyperplasia (CAH) due to P450c21 (21-hydroxylase deficiency) is a common autosomal recessive disorder. This disorder is due to mutations in the *CYP21A2* gene which is located at chromosome 6p21. The clinical features reflect the magnitude of the loss of function mutations. Individuals with complete loss of function mutations usually present in the neonatal period. The clinical features of individuals with mild loss of function mutations are predominantly due to androgen excess rather than adrenal insufficiency leading to an ascertainment bias favoring diagnosis in females. Treatment goals include normal linear growth velocity and "on-time" puberty in affected children. For adolescent and adult women, treatment goals include regularization of menses, prevention of progression of hirsutism, and fertility. This article will review key aspects regarding pathophysiology, diagnosis, and treatment of CAH.
Key Words: Congenital adrenal hyperplasia, Ambiguous genitalia, Premature pubarche, Hyperandrogenism, Premature adrenarche

Introduction

Congenital adrenal hyperplasia (CAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene. The earliest documented description was provided in 1865 by a Neapolitan anatomist named Luigi De Crecchio; he described a cadaver as having a penis with urethral openings on its underside, undescended testes, a vagina, a uterus, fallopian tubes, ovaries, and markedly enlarged adrenal glands.[1] This individual was reported to have behaved as a male throughout his adult life and died in his 40s during an episode of vomiting, diarrhea, and prostration. Just over 100 years later in 1957, the mild or nonclassical form of 21-hydroxylase deficiency was first described by Jacques Decourt, Max-Fernand Jayle, and Ettiene Baulieu.[2]

Since these descriptions, it has become apparent that the clinical features associated with CAH comprise a spectrum reflecting the consequences of the specific mutation. This continuum of 21-hydroxylase deficiency has been classified into salt wasting and simple virilizing forms, collectively referred to as classical 21-hydroxylase deficiency, and the milder nonclassical or late onset form.[3] The reported incidence of classical 21-hydroxylase deficiency ranges from 1 in 5000 to 1 in 15,000 with variation between ethnic/racial backgrounds.[4,5] For classical CAH, the carrier frequency is approximately one in 60 individuals. The prevalence is lower in African-Americans than in Caucasians in the United States.[6] The frequency of the nonclassical form is difficult to accurately determine due to problems of complete ascertainment. One study reported increased frequency among Hispanics, Yugoslavs, and Ashkenazi Jews.[4]

Etiology

In broad terms, the virilizing forms (simple virilizing or salt-wasting) of CAH are characterized by mutations that significantly impair cortisol biosynthesis and lead to the accumulation of steroid intermediates proximal to the deficient enzyme. The resulting loss of cortisol negative feedback inhibition leads to increased hypothalamic corticotrophin releasing hormone (CRH) and pituitary adrenocorticotrophic hormone (ACTH) secretion. With decreased P450c21 activity, conversions of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, and progesterone (P4) to deoxycorticosterone, respectively, are impaired. Elevated 17-OHP, P4, and androstenedione concentrations are typically found. The excessive ACTH stimulation also results in hypertrophy of the zona fasciculata and the zona reticularis, resulting in the adrenal hyperplasia typical of the syndrome, and possibly increased adrenocortical nodularity. Individuals with simple virilizing and nonclassical forms generally have adequate mineralocorticoid secretion.

Molecular Genetics

To date, 127 mutations have been reported in *CYP21A2* (http://www.hgmd.cf.ac.uk); these mutations range from complete loss of enzyme function to partial enzyme activity. Approximately 10–12 mutations account for the majority of the affected alleles; most of these common mutations result from recombination between the active gene, *CYP21A2*, and its highly homologous nonfunctional pseudogene, *CYP21A1P* (i.e., gene conversion). Both genes, *CYP21A2* and

* *Address correspondence to:* Selma Feldman Witchel, MD, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, 4401 Penn Ave, Pittsburgh, PA 15224
E-mail address: selma.witchel@chp.edu (S.F. Witchel).

1083-3188/$ - see front matter
doi:10.1016/j.jpag.2010.10.001

CYP21A1P, are located in close proximity within the HLA region on chromosome 6p21.3. The majority of the *CYP21A2* mutations reported to date are severe loss of function mutations associated with simple virilizing or salt-wasting classical CAH. Functional studies indicate that these mutations result in 0–5% residual enzymatic function.[7]

In general, phenotype correlates with molecular genotype and reflects the residual activity of the milder mutation.[8,9,10] Thus, patients with classical salt-losing CAH usually have complete loss of function mutations on both alleles. Patients with simple virilizing CAH often carry a complete loss of function mutation on one allele and I172N or the intron 2 splicing mutation on their other allele. Individuals with nonclassical congenital adrenal hyperplasia (NCAH) are often compound heterozygotes carrrying different *CYP21A2* mutations on each allele.

The missense mutation, V281L, accounts for at least one of the *CYP21A2* alleles for most patients with NCAH. This genetic variant is commonly identified among Eastern Europeans, especially those of Ashkenazi Jewish descent. Other missense mutations associated with NCAH include P30L, P453S, and R339H. Novel mutations associated with NCAH include R369W and I230T.[11] One half to two thirds of individuals with NCAH carry one allele encoding for a severe defect in enzyme function (which would result in classical CAH if present on both alleles) and an allele encoding a mild defect in enzyme function on the other allele.

Pathophysiology

Unfortunately, the pathophysiology of CAH is more complicated than would be suggested by an autosomal recessive disorder where the expression of the defective protein is limited to the adrenal cortex. For example, genetic variations at other loci may influence steroid metabolism and steroid responsiveness. Since steroid cells do not store large amounts of hormone, steroid hormone secretion reflects steroid hormone biosynthesis. Adrenal cortical steroidogenesis in CAH reflects the reactions catalyzed by *CYP21A2*, 3β-hydroxysteroid dehydrogenase type 2 (*3βHSD2*), cytochrome P450c17 (*CYP17A1*), and, to a small extent, P450c11β (*CYP11B1*).[12] The accumulation of steroid precursors due to the loss of P450c21 activity leads to increased concentrations of other steroid hormone intermediates.

One alternative steroid pathway particularly relevant to CAH is the so-called “backdoor pathway” or “alternative pathway.” While the 17,20-lyase activity of P450c17 towards Δ^4 substrates (conversion of 17-OHP to androstenedione) is not significant in humans, patients with CAH and NCAH may convert either P4 or 17-OHP to more potent androgens such as dihydrotestosterone (DHT).[13] In this alternative pathway, 17-OHP is catalyzed sequentially by 5α-reductase, the 17-20-lyase activity of P450c17, 17β-hydroxysteroid dehydrogenase, and 3α-hydroxysteroid dehydrogenase resulting in dihydrotestosterone (DHT) synthesis. For an affected female fetus, the elevated 17-OHP concentrations could potentially be diverted to DHT biosynthesis contributing to the genital ambiguity.[14,15]

Some *CYP21A2* missense mutations alter enzyme kinetics.[16] The mutated enzyme protein is synthesized, but is less efficient than the wild type. The net result is an increased precursor to product ratio, independent of ACTH levels. Hence P4 and 17-OHP levels in these patients may remain above normal even in the presence of excessive glucocorticoid administration.[17] It has been speculated that a dominant negative effect may also occur. Indeed, the concept of dominant negative activity with accumulation of steroid hormone intermediates has been offered as one explanation to explain the identification of mildly symptomatic heterozygotic carriers or so-called “manifesting heterozygotes”.[18–20]

Patients with NCAH usually have no evidence of ACTH or CRH excess. In fact, some have an over-responsive glucocorticoid response to ACTH stimulation, possibly reflective of subtle adrenal hyperplasia.[21] Among individuals with classical CAH, individuals with NCAH, heterozygotic carriers, and healthy control subjects, individuals with classical CAH demonstrated the highest oCRH-stimulated ACTH concentrations. These subjects showed a significant positive correlation between the oCRH-stimulated ACTH and 17-OHP responses.[22]

Alterations in hypothalamic-pituitary-ovarian (HPO) function with androgen excess and the appearance of a polycystic ovary-like phenotype may develop in women with CAH.[23,24] Potential etiologies include disruption of the hypothalamic-pituitary-ovarian (HPO) axis by persistently elevated progesterones (e.g., P4 and/or 17-OHP) or androgens, expression of 5α-reductase in the ovary, and/or a direct glucocorticoid effect. Androgen excess impairs hypothalamic sensitivity to progesterone resulting in a persistently rapid GnRH pulse frequency which favors luteininzing hormone (LH) hypersecretion.[25] This LH hypersecretion can initiate and maintain a vicious cycle in which excessive ovarian androgen secretion intensifies the consequences of the excessive adrenal androgen production. In fact, women with CAH demonstrate higher LH concentrations than normal women.[23] Prenatal programming of the hypothalamus due to excessive in utero androgen exposure may contribute to LH hypersecretion and reproductive dysfunction among women with classical forms of CAH.[26,27] However, in utero exposure to excessive androgens is unlikely to play a major role in the pathophysiology among women with NCAH.

Clinical Features by Age

Infants

Girls with classical forms (salt-losing or simple virilizing) generally present in the newborn period. Due to their exposure to androgens from approximately the sixth week of gestation, infant girls with classical CAH usually have ambiguous genitalia. Typical external genital physical findings include clitoromegaly, partially fused labia majora with rugae, and a common urogenital sinus in place of a separate urethra and vagina. The extent of virilization can range from a nearly male appearance of the external genitalia including a penile urethral meatus to minimal