Journal of Steroid Biochemistry & Molecular Biology 165 (2017) 2–11

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Steroid 21-hydroxylase deficiency in congenital adrenal hyperplasia

Alan A. Parsa[a,*], Maria I. New[b]

[a] Department of Medicine, University of Hawaii, John A. Burns School of Medicine, Honolulu, Hawaii, United States
[b] Adrenal Steroid Disorders Program, Icahn School of Medicine at Mount Sinai, Manhattan, NY, United States

ARTICLE INFO

Article history:
Received 14 January 2016
Received in revised form 26 June 2016
Accepted 30 June 2016
Available online 2 July 2016

Keywords:
21 hydroxylase deficiency
Congenital adrenal hyperplasia
CAH

ABSTRACT

Congenital adrenal hyperplasia (CAH) refers to a group of inherited genetic disorders involving deficiencies in enzymes that convert cholesterol to cortisol within the adrenal cortex. There are five key enzymes involved in the production of cortisol. Of these key enzymes, deficiency of 21-hydroxylase is the most commonly defective enzyme leading to CAH representing more than 90% of cases. The low adrenal cortisol levels associated with CAH affects the hypothalamic-pituitary-adrenal negative feedback system leading to increased pituitary adrenocorticotropic hormone (ACTH) production, which overstimulates the adrenal cortex in an attempt to increase cortisol production resulting in a hyperplastic adrenal cortex. The deficiency of enzyme 21-hydroxylase results from mutations or deletions in the CYP21A2 gene found on chromosome 6p. The disorder is transmitted as an autosomal recessive pattern and specific mutations may be correlated to enzymatic compromise of varying degrees, leading to the clinical manifestation of 21-hydroxylase deficiency (21-OHD) CAH.

Contents

1. Introduction

The first patient with clinical manifestations of CAH was described in literature in 1865 by Italian anatomist Luigi Decrecchio; he documented a case involving a male patient who died at the age of 44 from an apparent Addisonian crisis. Autopsy showed enlarged adrenal glands, stretched penile length of 10 cm,

* Corresponding author.
E-mail address: aparsa@hawaii.edu (A.A. Parsa).

http://dx.doi.org/10.1016/j.jsbmb.2016.06.015
0960-0760/

first degree hypospadias, no testes, normal ovaries, fallopian tubes, uterus and vagina [1,2]. Since the original description, more than 5 different forms of CAH have been described, of which 21-OHD is the most common, occurring in over 90% of cases. The hallmark of 21-OHD is the deficiency of enzyme 21-hydroxylase activity, leading to poor cortisol production and the subsequent accumulation of precursor steroid hormones in the steroidogenic pathway, resulting in hyperandrogenism. CAH owing to 21-OHD has been divided into two categories: classical and non-classical. The classical form is further divided into the salt wasting and simple virilizing form.

1.1. Embryologic

In the genetically normal female, the absence of anti-Müllerian hormone (AMH), allows for normal Müllerian structure development (fallopian tubes, uterus, cervix, upper 2/3 of vagina); the absence of testicular tissue and androgens, leads to regression of Wolffian structures; and the ovaries remain in the pelvis.

In 21OHD, a genetically female fetus lacks AMH, preserving Müllerian structure development, and the ovaries remain within the pelvis. Testosterone may be elevated, not from fetal Leydig cells of the testes, but from adrenal androgen production [3]. The accumulation of steroid precursors to the defective enzyme, 21-hydroxylase, will shunt to the androgen pathway producing testosterone (Fig. 1). The degree of enzyme dysfunction will dictate the degree of shunting. External genitalia development is sensitive to androgens, thus high circulating testosterone levels leads to masculinization of fetal external genitalia to variable degrees as described by the Prader score (Fig. 2).

1.2. Classical CAH

Classical CAH is an inherited disorder affecting 1:13,000 to 1:15,000 live births and is represented by two phenotypes: simple-virilizing (SV) and salt wasting (SW). SW CAH, the more severe of the two, accounts for an estimated 75% of classical cases [4]. SW CAH, is caused by the severe impairment of 21-hydroxylase enzyme (<2% enzymatic activity), leading to inadequate production of aldosterone and cortisol to sustain life. The lack of aldosterone, required for sodium homeostasis, if left untreated, will lead to hypovolemia, hyponatremia, hyperkalemia, hyperreninemia, failure to thrive, seizure, and ultimately death in a newborn occurring as early as one to four weeks from delivery. Early detection is imperative to survival and amplifies the importance of newborn screenings. Newborn males, born without genital ambiguity to raise suspicion, are particularly at risk. If missed by newborn screen, males could be discharged home where they will experience a salt wasting/adrenal crisis and potential death. An afflicted adult who suddenly stops taking mineralocorticoid replacement therapy will experience a similar fate. Females, with classical CAH, are born with ambiguous genitalia prompting further evaluation and treatment. Routine monitoring of an affected individual's mineralocorticoid balance, with plasma renin activity and serum aldosterone levels, will assure appropriate therapy and evaluate potential improvement of the salt wasting state with age [5]. Glucocorticoid deficiency will persist into adulthood and may lead to poor cardiac function, poor vascular tone. In addition, catecholamine deficiency can occur [6].

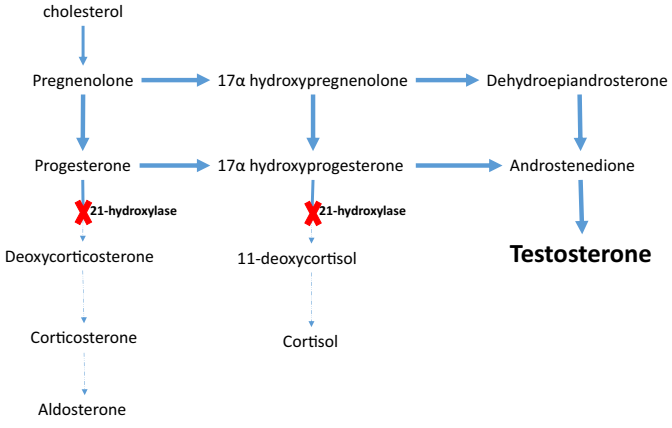

Fig. 1. Deficiency of enzyme 21-hydroxylase leads to the accumulation of precursor enzymes and the shunting to testosterone production.

An increase of about 1–2% of enzyme 21-hydroxylase activity, compared to SW CAH, leads to SV CAH. SV CAH encompasses around 25% of all classic CAH patients. Similar to SW CAH, accumulation of precursor steroids leads to overproduction of adrenal androgens and variable degrees of genital virilization in a genetic female fetus and no genital ambiguity in the genetic male fetus. In SV CAH, Aldosterone is produced in adequate amounts preventing a salt wasting crisis, making mineralocorticoid replacement therapy unnecessary. Since both SV and SW CAH can present with female genital ambiguity, patients are sometimes treated as salt wasters with both mineralocorticoid and glucocorticoid supplementation until a final diagnosis is made.

During postnatal development, if not treated appropriately with glucocorticoids, both males and females with classical CAH will develop signs of androgen excess including precocious pubarche and adrenarche, acne, rapid linear growth, and advanced bone age leading to a short final height [7,8]. Testicular adrenal rest tumors (TART), a potential complication in males, present with a variable prevalence rates between 18 and 100% [9–11]. Detection methods for TARTs vary from palpation, ultrasonography, or magnetic resonance imaging. The etiology and contributing factors of TARTs has yet to be established. It has been hypothesized that chronic overstimulation of adrenal tissue remnants in the testicles, which normally regresses before birth, lead to TART formation [12,13]. Later in life, poor hormonal control leads to enlarged TARTs affecting fertility [14,15].

1.3. Non-Classical CAH

Non-classical 21-OHD (NCCAH) refers to a partial 21 hydroxylase enzyme deficiency, typically around 20–50% normal enzyme function [16]. Cortisol and aldosterone produced by the adrenal cortex prevent clinical deficiencies requiring glucocorticoid or mineralocorticoid replacement therapy. Though not requiring therapy for survival, the cortisol production by the adrenal glands is insufficient to adequately suppress ACTH over secretion and the shunting of precursor steroids lead to hyperandrogenemia (Fig. 1).

At birth, individuals with NCCAH have normal genitalia with normal baseline 17-hydroxyprogesterone levels. It is common for individuals with NCCAH to remain undiagnosed experiencing normal growth, puberty, and reproduction, coming to attention only as a result of kindred studies [17]. Presenting signs of NCCAH in children may include premature pubarche [18,19], premature adrenarche [20], cystic acne [21], accelerated growth [22], and/or advanced bone age [23,24]. Growth may eventually be arrested in these patients due to early epiphyseal fusion compromising final height (tall children with short final height) [25]. Later in life, common presenting features are hirsutism (60–78%), menstrual cycle disorders (55%), acne (33%) and decreased fertility (12%) [26,27]. These features are likely secondary to excess androgens in circulation. Male features are less evident remaining asymptomatic or present with acne and/or impaired fertility.