Steroids 78 (2013) 747–750

Contents lists available at SciVerse ScienceDirect

Steroids

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

# Non-classic congenital adrenal hyperplasia ☆

Selma Feldman Witchel *

*Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA*

ARTICLE INFO

*Article history:*
Received 3 April 2013
Received in revised form 5 April 2013
Accepted 5 April 2013
Available online 28 April 2013

*Keywords:*
Non-classic congenital adrenal hyperplasia
Late-onset congenital adrenal hyperplasia
Hirsutism
Androgen excess
Polycystic ovary syndrome

ABSTRACT

Non-classic or late-onset congenital adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive disorders. Reported prevalence is approximately 1 in 1000. Affected individuals typically present due to signs and symptoms of androgen excess. The purpose of this review is to provide current information regarding the pathophysiology, molecular genetics, and management of this common disorder. The treatment of NCAH needs to be directed towards the symptoms. For affected children, goals of treatment include normal linear growth velocity, normal rate of skeletal maturation, "on-time" puberty. For affected adolescent and adult women, goals of treatment include regular menstrual cycles, prevention or progression of hirsutism and acne, and fertility. Treatment needs to be individualized and should not be initiated merely to decrease abnormally elevated hormone concentrations.



**Contents**



## 1. Introduction

Congenital adrenal hyperplasia (CAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene located at chromosome 6p21.3. The earliest documented description of CAH 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 identified as a male throughout his adult life and died in his 40's during an episode of vomiting, diarrhea, and prostration. Just over 100 years later in 1957, the mild or non-classical form of 21-hydroxylase deficiency was first described by Jacques Decourt, Max-Fernand Jayle, and Ettiene Baulieu [2].

CAH is classified into three categories even though disease severity represents a spectrum [3]. The salt-losing form is characterized by life-threatening glucocorticoid and mineralocorticoid deficiencies; affected female infants are generally identified by genital ambiguity. Manifestations of the simple virilizing form include glucocorticoid deficiency and virilization of female infants without overt salt loss. Individuals with NCAH typically present in late childhood, adolescence, or adulthood with signs and symptoms of excessive androgen secretion [4]. The reported prevalence of NCAH is 1 in 1000 [5]. However, the frequency is higher among specific ethnic groups such as Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations [6].

☆ Presented in part at the Androgen Excess-Polycystic Ovary Syndrome Society 10th Annual Meeting, Beijing, China, September 21–23, 2012.

* Tel.: +1 412 692 5170; fax: +1 412 692 5834.
*E-mail address:* witchelsf@upmc.edu

0039-128X/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2013.04.010

Unfortunately, the pathophysiology of CAH is more complicated than would be suggested for an autosomal recessive disorder where the expression of the defective protein is limited to a single tissue, the adrenal cortex. Genetic variations at other loci may influence steroid biosynthesis, metabolism, and hormone responsiveness. Since steroid producing cells do not store large amounts of hormone, steroid hormone secretion reflects steroid hormone biosynthesis. Adrenal cortical steroid hormone secretion integrates the reactions catalyzed by P450c21, 3β-hydroxysteroid dehydrogenase type 2 (*3βHSD2*), cytochrome P450c17 (*CYP17A1*), and, to a small extent, P450c11β (*CYP11B1*) [7]. In 21-hydroxylase deficiency, the accumulation of steroid precursors proximal to the dysfunctional P450c21 protein leads to increased concentrations of other steroid hormone intermediates.

During adolescence and adulthood, an ascertainment bias favors the diagnosis of NCAH in females due to the nature of the hyperandrogenic symptoms. Symptoms include hirsutism, acne, androgenic alopecia, anovulation, menstrual dysfunction, and infertility. In a multi-center study, the most common symptoms among adolescent and adult women were hirsutism (59%), oligomenorrhea (54%), and acne (33%) [8]. Among 161 women with NCAH, presenting symptoms were hirsutism (78%), menstrual dysfunction (54.7%), and decreased fertility (12%) [9]. Prepubertal children, both girls and boys, can present with tall stature, advanced skeletal maturation, and premature development of pubic hair, axillary hair, and adult apocrine odor. Girls may develop clitoromegaly. Boys may have penile enlargement with prepubertal testes.

Not all individuals with NCAH will be symptomatic. A study of the phenotype/genotype relationship in 330 family members revealed 9 symptomatic affected individuals, 42 clinically asymptomatic affected individuals, 242 heterozygotic carriers, and 37 unaffected individuals [9]. As reported in this study, affected males are generally asymptomatic and usually identified following the diagnosis of a female family member. Indeed, parents of children with CAH may have undiagnosed asymptomatic NCAH [10]. Peripubertal gynecomastia and adrenocortical incidentaloma are extremely uncommon presenting features for males [11,12].

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 [13,14]. Possible explanations include disruption of the hypothalamic–pituitary–ovarian (HPO) axis by persistently elevated progesterones (e.g. progesterone [P4] and/or 17-hydroxyprogesterone [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 luteinizing hormone (LH) hypersecretion [15]. This LH hypersecretion can initiate and maintain a vicious cycle in which LH stimulates excessive ovarian theca cell androgen secretion exacerbating the consequences of the excessive adrenal androgen production. In fact, women with CAH demonstrate higher LH concentrations than normal women. Prenatal programming or imprinting 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 [16,17]. However, the lack of virilization of the external genitalia of female infants with NCAH suggests that in utero exposure to excessive androgens is unlikely to play a major role in the hypothalamic imprinting among women with NCAH.

## 2. Diagnosis

The clinical features of NCAH in postpubertal women may be difficult to differentiate from those of the polycystic ovary syndrome (PCOS) or, in children, from premature adrenarche. Although random 17-OHP concentrations are usually diagnostic in classical forms of CAH, random 17-OHP concentrations may be within the normal range for individuals with NCAH. Thus, the acute ACTH stimulation test remains the gold standard to confirm decreased 21-hydroxylase activity. Following collection of a blood sample to measure baseline hormone concentrations, synthetic ACTH (Cortrosyn, 0.25 mg) is administered. A second blood sample is collected 30–60 min later.

Correlation of hormone concentrations with genetic analyses has suggested that mutations are likely to be identified on both alleles when the ACTH-stimulated 17-OHP value exceeds 1500 ng/dl, although a few NCAH patients, particularly if older, will demonstrate ACTH-stimulated 17-OHP levels between 1000 and 1500 ng/dl. In one study, among 123 women with NCAH confirmed by molecular *CYP21A2* analysis, mean basal 17-OHP and mean ACTH-stimulated 17-OHP concentrations were 1300 ± 1420 ng/dl and 4080 ± 2040 ng/dl, respectively [9]. 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 [18].

Since it is impractical to perform an acute ACTH stimulation test in all women and children suspected of NCAH (e.g. those with hyperandrogenic features or ovulatory/menstrual dysfunction), some investigators have suggested the use of unstimulated 17-OHP concentrations [19–21]. In general, 17-OHP concentrations between 170–300 ng/dl have been found to be useful as a screening tool to indicate need for additional evaluation; this blood sample should be obtained in the morning and, most importantly (to reduce false positives), in the follicular phase of the menstrual cycle. Among 129 Portuguese women with hyperandrogenism and menstrual dysfunction, 87% of women with NCAH, 25% of lean women with PCOS, 20% of obese women with PCOS, and 7% of control women had basal 17-OHP concentrations >200 ng/dl [22]. In childhood, NCAH may present with premature adrenarche. In a group of 238 French children with premature pubic hair, of which 4.2% had NCAH, the use of a 17-OHP cut-off value of greater than 200 ng/dl provided a 100% sensitivity and 99% sensitivity for the detection of NCAH in this cohort [23].

## 3. Genetics

When considering genetic testing, the complexity of the *CYP21A2-CYP21A1P* loci confounds molecular genetic analysis [24]. Multiple mutations can occur on one allele so that the identification of two mutations does not always signify CAH because both mutations may occur on the same allele (*cis*). Copy number variation involving the *CYP21A2-CYP21A1P* region may result in multiple copies of *CYP21A2* on a single allele. Using multiplex ligation-dependent probe amplification, the Q318X mutation has been reported in association with a duplicated *CYP21A2* allele. In other words, one allele carries both a normal *CYP21A2* gene and a *CYP21A2* gene with Q318X mutation. This specific allele, often associated with the HLA haplotype HLA-B ∗ 50-Cw- ∗ 06, is presumed to represent a founder effect and illustrates the complexity of *CYP21A2* genetic analyses [25].

Most commercially available screening panels assay for the 10–12 most common mutations, and may not be able to detect all mutations [26]. Inclusion of a DNA sample from at least one parent and/or a child will help to discriminate between variants on the same (*cis*) or different (*trans*) alleles. Genetic testing should not be considered a first-line diagnostic study in individuals suspected of CAH or NCAH. However, genetic studies may be useful for affected individuals (men or women) and their siblings for reproductive planning concerns. Genetic testing can identify those individuals who are com-