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# Recommendations for Treatment of Nonclassic Congenital Adrenal Hyperplasia (NCCAH): an Update

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## Abstract

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders. 21-hydroxylase deficiency, in which there are mutations in *CYP21A2* (the gene encoding the adrenal 21-hydroxylase enzyme), is the most common form (90%) of CAH. In classic CAH there is impaired cortisol production with diagnostic increased levels of 17-OH progesterone. Excess androgen production results in virilization and in the newborn female may cause development of ambiguous external genitalia. Three-fourths of patients with classic CAH also have aldosterone insufficiency, which can result in salt-wasting; in infancy this manifests as shock, hyponatremia and hyperkalemia. CAH has a reported incidence of 1:10,000–1:20,000 births although there is an increased prevalence in certain ethnic groups. Nonclassic CAH (NCCAH) is a less severe form of the disorder, in which there is 20–50% of 21-hydroxylase enzyme activity (vs. 0–5% in classic CAH) and no salt wasting. The degree of symptoms related to androgen excess is variable and may be progressive with age, although some individuals are asymptomatic. NCCAH has an incidence of 1:1000–1:2000 births (0.1–0.2% prevalence) in the White population; an even higher prevalence is noted in certain ethnic groups such as Ashkenazi Jews (1–2%). As many as two-thirds of persons with NCCAH are compound heterozygotes and carry a severe and mild mutation on different alleles. This paper discusses the genetics of NCCAH, along with its variable phenotypic expression, and reviews the clinical course in untreated patients, which includes rapid early childhood growth, advanced skeletal age, premature adrenarche, acne, impaired reproductive function in both sexes and hirsutism as well as menstrual disorders in females. Finally, it addresses treatment with glucocorticoids vs. and other alternatives, particularly with respect to long term issues such as adult metabolic disease including insulin resistance, cardiovascular disease, metabolic syndrome, and bone mineral density.

### Keywords

21-hydroxylase deficiency; nonclassic congenital adrenal hyperplasia; androgen excess; hirsutism

## Introduction

The term congenital adrenal hyperplasia (CAH) describes a group of disorders in which there is impaired cortisol synthesis secondary to a deficiency in one of the enzymes



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necessary for cortisol production [1]. As a result of the disordered enzymatic step, cortisol production is decreased, adrenocorticotropic hormone (ACTH) is increased via a negative feedback loop, and there may be overproduction of the hormones before the enzymatic block and/or deficiency of the hormones distal to the block. CAH is an uncommon disorder with an incidence of 1:10,000 to 1:20,000 births, although there is an increased prevalence in certain ethnic groups [2–5].

The most common form of CAH is 21-hydroxylase deficiency, which is caused by mutations in *CYP21A2*, the gene that encodes the adrenal 21-hydroxylase enzyme located in close proximity within the HLA region on chromosome 6p21.3 [1,6,7]. 21-hydroxylase deficiency accounts for greater than 90% of all patients with CAH. As a result of the deficient enzyme, the conversions from 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone are impaired. Symptoms of CAH vary depending upon which hormones are deficient and which are produced in excess. In the classic form of 21-hydroxylase deficiency, there is not only impaired cortisol production, but also excess androgen production that can cause virilization. Seventy-five percent of CAH individuals will also have aldosterone deficiency, which can cause a salt-wasting crisis in infancy manifest by significant hyponatremia, hyperkalemia, and shock [8].

A less severe form of the disorder, nonclassic CAH (NCCAH), has also been described in which there is 20–50% of 21-hydroxylase activity compared to 0–5% in classic CAH [9,10]. With NCCAH, salt-wasting is absent and affected females most commonly have normal genitalia at birth [11]. NCCAH individuals may show evidence of androgen excess in childhood or adulthood, although there are a number of persons who remain asymptomatic. Nonclassi c CAH is much more prevalent a disorder than classic CAH; it is estimated that 1 in 1000 (0.1–0.2% prevalence) non-Jewish Caucasian individuals of mixed ethnicity are affected and as many as 1 in 30 among Ashkenazi Jews (1–2% prevalence) [12]. Mutations in *CYP21A2* account for most cases of NCCAH, although mutations in 11β-hydroxylase (*CYP11B1*) and 3β-hydroxysteroid dehydrogenase (*HSD3B2)* have also been described [13,14]. This review focuses on NCCAH due to 21-hydroxylase deficiency, with an emphasis on the genetics, diagnosis, clinical progression, and issues related to treatment for this disorder.

## Genetics

As of 2010, 181 mutations have been reported in the *CYP21A2* gene [15]. Recombination events between *CYP21A2*, the active gene, and a highly homologous pseudogene, *CYP21A1P*, account for most mutant alleles, with 10–12 mutations explaining the majority of affected alleles [9]. Classic salt-wasting CAH often is the result of a large gene deletion and a splicing mutation in the second intron, while there are few alleles that are specific to NCCAH [16]. Mutations in *CYP21A2* that are associated with classic CAH, both salt-wasting and simple virilizing, result in a 95–100% loss of enzymatic activity [10]. In the case of NCCAH, there is typically a 50–80% loss of enzyme activity [9].

Individuals with NCCAH most commonly are compound heterozygotes with different *CYP21A2* mutations on each allele. As such, the less severe allele typically determines the phenotype [17]. Seventy percent of NCCAH individuals carry a point mutation, Val281Leu, at exon 7 that retains 20–50% of the enzyme activity [18–20]. This V281L mutation is found in the majority of Eastern European Jewish cohorts, as well as in many other ethnic groups except for the Japanese [21,22]. The P30L allele tends to result in a clinical picture of more pronounced androgen excess [23]. P453S and R339H are also associated with NCCAH [9]; R369W and I230T are two novel mutations associated with NCCAH [24].

## Diagnosis

Making the diagnosis of NCCAH is not nearly as straightforward as in the case of classic CAH. While newborn screening has been shown to be of enormous benefit in the case of classic disease and affected females typically come to attention as a result of genital ambiguity, most screening programs do not detect those individuals with NCCAH [25]. In addition, a number of individuals with NCCAH remain asymptomatic and experience normal growth, puberty and have normal reproductive function, only coming to attention as a result of kindred studies [11]. Thus, most of what is known about NCCAH is due to referral of patients who experience symptoms of androgen excess. It is also possible that patients with both classic CAH and NCCAH demonstrate signs of androgen excess from alternate "back-door" pathway formation of dihydrotestosterone (DHT) from 5α and 3α reduction of elevated 21-carbon precursors (i.e., progesterone and 17-OHP) [26].

In children less than 10 years of age, the most common symptom at presentation is premature pubarche, which is the appearance of pubic hair in girls less than 8 years and in boys less than 9 years of age [27]. Older children may also present with tall stature, advanced skeletal age, and increased linear growth velocity. In adolescence and adulthood, symptoms of androgen excess tend to favor the diagnosis of NCCAH in females as compared to males [28]. Other possible symptoms include hirsutism, acne, menstrual irregularities, androgenic alopecia, and infertility. The progressive nature of the disease is highlighted by the fact that the prevalence of hirsutism has been shown to increase with age and has been noted to be rare before puberty [27]. It is important to note that most if not all patients who present for evaluation will exhibit symptoms related to androgen excess, not to deficient cortisol production.

The gold standard for diagnosis remains the ACTH (cosyntropin) stimulation test. Baseline samples are collected for 17-OHP and cortisol after which synthetic ACTH (cosyntropin) is administered with a standard dose of 250 μg for older children and adults. Repeat blood work is collected 60 minutes after administration to determine the stimulated values of both 17-OHP and cortisol. While stimulated 17-OHP levels with classic CAH typically exceed 20,000 ng/dl, those with NCCAH will have 17-OHP levels within the range of 1,500–10,000 ng/dl post stimulation [29]. Cortisol levels are collected to document adrenal reserve.

In clinical practice, it is not feasible to administer ACTH stimulation tests on all individuals suspected of having NCCAH who in fact have clinical symptomatology that closely mirror that of PCOS or other androgenic conditions. Instead, it has been proposed to use baseline non-stimulated values of 17-OHP as a screening tool for possible NCCAH [30–33]. The recent Endocrine Society guidelines recommend obtaining early morning serum (7:30am–8:00am) 17-OHP levels in symptomatic patients [34]. Random measurements of 17-OHP have not been shown to be helpful since these often yield normal levels in patients with NCCAH [32]. Morning 17-OHP levels of > 200 ng/dl should prompt further evaluation since it has been shown that levels above 200 ng/dl capture 90% NCCAH individuals [27,32]. Genetic testing is not considered to be a primary diagnostic tool for NCCAH at this time, but may be helpful in the setting of borderline results or for genetic counseling purposes [16].

## Risk in Offspring

Congenital adrenal hyperplasia is an autosomal recessive disorder. As stated, the incidence of classical CAH is 1:10,000–1:20,000, thus the incidence of carriers in the general population is 1:50–1:71 with a median of 1:60. As such, a patient with classic CAH would be predicted to have a 1 in 120 chance of having a child with classic CAH. Since most patients with NCCAH carry one allele with a severe mutation for *CYP21A2*, there is a risk

for having offspring with classic CAH. A parent with NCCAH would be predicted to have a 1 in 240 chance of having a child with classic CAH, (1/60 × ½) × (1 × ½) [34]. Since two-thirds of NCCAH patients are compound heterozygotes, the predicted incidence may be closer to 1 in 360, (1/60 × ½) × (2/3 × ½). However, a study of pregnancy outcomes among 101 women with NCCAH demonstrated that the risk of giving birth to a child with classic disease is a much more frequent occurrence at 2.5% and at least 15% of the offspring will have NCCAH [31]. Moran et al have suggested that this may be due to the high rate of intermarriage in certain at risk ethnic subpopulations [31].

## Clinical Picture/Treatment Options

Many patients with NCCAH are asymptomatic and current recommendations argue against treatment for those without symptoms. In symptomatic patients, the signs and symptoms of NCCAH vary with age. As stated, in the newborn period, female infants with NCCAH are not typically born with ambiguity of the external genitalia. Premature development of pubic hair has been reported as early as 6 months [11] and in as many as 60% of persons with NCCAH [27]. Of interest is that in children with premature adrenarche, the incidence of NCCAH is reported to be from 5–30% [35,36]. It is not clear which patients with NCCAH will advance to have frank hirsutism and acne or have additional signs of androgen excess, such as rapid growth and bone age advancement which is associated with premature adrenarche itself [37]. Advancement of bone age and tall stature in childhood can result in truncated final height due to rapid fusion of epiphyses. Although studies have shown this in both classic CAH and NCCAH [38], most NCCAH children have normal height for their families and those with truncated final height have had inappropriate early onset or rapid progression of pubarche or bone age [34]. Issues of final height are also related to suppressive effects of glucocorticoid treatment. Adult height approaching expected target height has been reported in patients who adhere to strict monitoring [39–41]. The current guidelines on CAH suggest treating children with NCCAH who have inappropriately early onset or rapid progression of pubarche or bone age. Further, treatment with GnRH analogs and GH prescription if begun before age 12 has resulted in attainment of target height, as demonstrated by Lin-Su et al [42]. However, such therapy is not routinely recommended by the new CAH guidelines [34] except if the predicted height SD is minus 2.25 or below their target height. Further, if used, these therapies should be considered as experimental treatment approaches and part of formally approved clinical trials.

## Hirsutism/Cystic Acne/Balding

In a multicenter review by Moran et al [27] reviewing the distribution of symptoms in 220 women from 11 centers, hirsutism after the age of 10 years was present in 59% and acne in 33% of women. In fact, the presence of hirsutism correlated ($r=0.97$, $p<0.02$) with increasing age, supporting the fact that NCCAH is a progressive disorder in some individuals. The prevalence of alopecia also appeared to increase with age: 6% of 10–19 year olds affected as compared to 19% of 40–49 year olds. Male pattern balding in females has been reported to be the sole symptomatic sign of NCCAH [43]. In a recent paper on androgenic alopecia, out of 57 pediatric patients, one 11 year old male was found to have NCCAH [44]. Similarly, 3 patients with acne that was refractory to treatment were shown to have NCCAH and responded to glucocorticoid therapy [45]. In one small study, treatment with dexamethasone 0.25 mg orally every evening reversed acne in 3 months but hirsutism required up to 30 months of treatment for resolution [46]. Treatment would then be recommended based on the severity and progression of symptoms.

## Menstrual Irregularity, Fertility and Reproductive Issues

In women, menstrual irregularities can be a presenting sign of NCCAH, although in a large series of women (n=950) referred for evaluation of androgen excess, NCCAH only accounted for about 4% of the etiology. Of note in this series, 56% and 72.8% of women by NIH and Rotterdam criteria for PCOS, respectively, would be considered to have PCOS (77% of the hyperandrogenic women had polycystic ovaries) [47]. Similarly, another recent study assessed 270 women with presenting signs of hyperandrogenism; 6 (2.2%) were confirmed to have NCCAH by genotyping. The cutoff sensitivity for baseline17-OHP was 172 ng/dl showing a 100% sensitivity and 88.6% specificity [48]. On the other hand, if one examines women with NCCAH, oligomenorrhea is more common than primary amenorrhea. Moran et al examined 220 women with NCCAH and between the ages of 10 and 19 years, the prevalence of oligomenorrhea was as high as 56% compared to only 9% of adolescents who experienced primary amenorrhea [27].

The issue of fertility in patients with NCCAH is important, since according to a cohort study of 203 patients with CAH, 34 women had NCCAH. The success rate of women with NCCAH seeking pregnancies was 67% vs. 54% for those with classic CAH [49]. Two large studies have previously suggested that “subfertility” is mild in NCCAH. Moran et al reviewed the outcomes of 203 pregnancies in 101 women with NCCAH [31]. Of note, 68% occurred prior to the diagnosis of NCCAH. Of significance was the fact that spontaneous miscarriages occurred in 25% (35/138) vs. 6% (4/65) of pregnancies after diagnosis and treatment. Similarly, Bidet et al studied 190 women with NCCAH [50]. Only 12% had sought consultation for infertility. 52.9% had pregnancies that occurred prior to diagnosis of NCCAH. The rate of miscarriage was 6.5% for pregnancies with glucocorticoid treatment vs. 26.3% without. Overall of 95 women who desired pregnancy within one year, 76% were successful, which was somewhat less than their control population whose success rate was 92% at one year. However, the cumulative pregnancy incidence of 83.5% resulting in birth (n=88 live births out of 101 pregnancies, 82%) was no different than their reported control group. In a smaller study in which 6 women had NCCAH, 50% had children at the time of their study. Of interest in this small study, an unexplained decrease in male offspring was noted in patients with CAH [51]. The recommendation from the 2010 guidelines [34] is to treat adults with NCCAH who demonstrate “patient important” hyperandrogenism or infertility.

Fertility in males with NCCAH has been less studied than in females. Although oligospermia has been reported, overall it appears that men with NCCAH have relatively normal gonadal function and sperm counts, although this may be due to under-diagnosis of NCCAH in males [52,53]. Infertility seems to be reversed with glucocorticoid therapy [52]. Further, although ectopic adrenal rests located in the testes (TARTS) may be associated with low sperm counts or Leydig cell failure, these are more commonly associated with classic CAH. Treatment with glucocorticoids can reverse the findings, both of the masses and infertility [54].

## Obesity/Metabolic Syndrome and Bone Mineral Density (BMD)

It is known that children with classic CAH have increased fat mass compared to controls [46]. Limited data are available on obesity, hypertension and insulin resistance in patients with NCCAH. Speiser et al reported on insulin sensitivity in patients with NCCAH [56]. Frank glucose intolerance was not observed in this small study. At the present time, even with limited data, healthy lifestyle counseling should begin early to prevent an increase in body fat and metabolic dysregulation. Data are beginning to emerge regarding BMD in patients with classic CAH, but are difficult to interpret because of variability in dosing of

glucocorticoids and degree of androgen excess/degree of control [57]. Data are not analyzed for NCCAH. Current guidelines suggest that children with CAH should not have BMD testing [34]; however it would seem prudent to maintain adequate intake of vitamin D in all growing persons and women of reproductive ages.

## Prenatal Treatment

At the present time, prenatal treatment is still considered experimental. As such, even if genotyping of a fetus suggests a classic mutation in a female (i.e. NCCAH mother is compound heterozygous and partner is also compound heterozygous, thereby the potential for having 2 severe gene mutations in a female fetus), prenatal treatment should be undertaken only in centers with protocols approved by Institutional Review Boards and the risks/benefits of the procedures be adequately discussed with the family [34]. There is one report by New in which the mothers of 9 fetuses genotyped (one by HLA) to have NCCAH received prenatal treatment from as early as 4 weeks gestation; treatment was continued until week 41 of gestation in 5 patients [58]. No difference was noted in the genitalia in those treated with dexamethasone and all were normal.

## Treatment of NCCAH

As stated above, unless the individual is symptomatic, treatment is not always indicated. Treatment is recommended to reduce symptomatic hyperandrogenism with low dose glucocorticoids, as in children with early onset and rapid progression of pubic and body hair, rapid growth and/or skeletal advancement. Although oligomenorrhea responds to glucocorticoid treatment, hirsutism is more difficult to remedy, requiring long-term medical management combined with other modalities, including electrolysis and/or laser treatment.

Steroid treatment in children is usually hydrocortisone 10–15 mg/m$^2$ divided into three doses daily, although lower doses are often effective. Overdosing can result in poor growth and Cushingoid features. Adolescents often are treated with longer acting steroids. Stress dosing of steroids for NCCAH is recommended as in classic CAH for patients who are glucocorticoid treated. However, persons with NCCAH who have a normal cortisol response to ACTH stimulation are usually not treated with stress doses for illness or surgical procedures [34].

Even in patients with NCCAH who are treated with glucocorticoid therapy, stress dosing is not needed in the setting of mental or emotional stress, minor illness or before physical exercise. In addition, patients with NCCAH do not require mineralocorticoid therapy, as they do not exhibit salt-wasting. Finally, it is recommended that previously treated patients with NCCAH be given the option of discontinuing therapy if symptoms resolve [34].

## Summary

Nonclassic CAH is a less severe form of CAH in which 20–50% of 21-hydroxylase activity is retained. It is a much more prevalent disorder than classic CAH. While a number of individuals with NCCAH appear to remain asymptomatic, others may present for medical evaluation as a result of signs and symptoms of androgen excess in both childhood and adulthood. Potential signs include premature pubarche, rapid growth and advanced skeletal maturation, hirsutism, acne, menstrual irregularities and reproductive issues. Although the 17-OHP response to ACTH stimulation testing remains the standard for diagnosis, early morning baseline values of 17-OHP have been shown to be a good initial screening test in symptomatic patients. Values > 200 ng/dl should prompt further evaluation. At this time, treatment with glucocorticoid therapy is typically only recommended for those individuals with symptomatic hyperandrogenism. Genetic counseling for those with NCCAH is

important given the increased risk for having offspring with the classic form of the disorder. Although there have been many advances in recent years, there is still much to learn about the optimal management and treatment of individuals with both classic and nonclassic forms of CAH.

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## Highlights

- Nonclassic congenital adrenal hyperplasia (NCCAH) is a less severe form of CAH.
- Individuals with NCCAH may come to attention as a result of excess androgen production.
- Early morning baseline 17-OHP values have been shown to be a good initial screening test for NCCAH.
- Glucocorticoid therapy is currently only recommended for the symptomatic individual.
- Genetic counseling for NCCAH patients is important, given the risk for having offspring with classic CAH.