21-Hydroxylase Deficiency

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Abstract
Steroid 21-hydroxylase deficiency is a relatively common disorder in humans. It accounts for about 95% of cases of congenital adrenal hyperplasia (CAH), which is seen in about 1 of every 15,000 live births worldwide. Newborns are currently being screened for the classical forms of this disease throughout the United States and in 12 other countries. Non-classic 21-hydroxylase deficiency (NC21OHD) is believed to affect one percent of the general population. Symptoms of NC21OHD are similar to polycystic ovarian syndrome (PCOS) in women, and include severe acne and loss of scalp hair in both sexes, and hirsutism in women.

21-Hydroxylase

21-Hydroxylase (21-OH) catalyses the hydroxylation (adding an "–OH") of the carbon atom 21 in steroids, which converts:

- Progesterone into Deoxycorticosterone, which is a precursor of aldosterone
- 17-OH Progesterone into 11-Deoxycortisol, which is a precursor of cortisol and cortisone.
Figure 1: Steroid Metabolism

5AR = 5alpha-Reductase
5BR = 5beta-Reductase
17-OH = 17-Hydroxylase
21-OH = 21-Hydroxylase
3β-HSD = 3beta-Hydroxysteroid reductase
11β-HSD = 11beta-Hydroxysteroid reductase

THA = 11-Dehydrotetrahydrocorticosterone
THB = Tetrahydrocorticosterone
5α-THB = Allo-Tetrahydrocorticosterone
THE = Tetrahyrdocortisone
THF = Tetrahydrocortisol
21-Hydroxylase Deficiency

Steroid 21-hydroxylase deficiency is a relatively common disorder in humans. It accounts for about 95% of cases of congenital adrenal hyperplasia (CAH), which is seen in roughly 1 of every 15,000 live births worldwide. Newborns are currently being screened for the classical forms of 21-OH deficiency throughout the United States and in 12 other countries. (Speiser, Azziz et al. 2010)

A defect within the CYP21B gene causes a disturbance of the development of the enzyme, which leads to congenital adrenal hyperplasia due to 21-hydroxylase deficiency. A related pseudo-gene is located near this gene, and gene conversion events involving the functional gene and the pseudo-gene are thought account for many cases of steroid 21-hydroxylase deficiency.

Non-Classic Deficiency

One percent of the general population is said to have non-classic 21-hydroxylase deficiency (NC21OHD). NC21OHD occurs with increased frequency in certain ethnic groups, such as Ashkenazi Jews, in whom one in 27 express the disease. NC21OHD is a widely under-diagnosed disorder in children and adults. (New 2006)

A partial deficiency of 21-hydroxylation causes postnatal androgen excess in patients of both sexes, leading to various hyper-androgenic signs that manifest from childhood to adulthood. In men manifestations of adrenal androgen excess may include short stature or oligospermia and diminished fertility. Women with NC21OHD can suffer from gonadal dysfunction and menstrual disorders including amenorrhea, anovulation, oligomenorrhea, and infertility. Previous studies suggest that these irregularities may be due to the conversion of excess adrenal androgens to estrogens, which then disrupt gonadotropin secretion. (New 2006)

Although hyper-androgenic signs in NC21OHD are not fatal, they can be troublesome for many patients. Severe acne in adolescents is often disabling, causing young patients to withdraw from social function. Loss of scalp hair in females and males is embarrassing, requiring treatment with 5alpha-reductase inhibitors and other hair-restoring treatments. Hirsutism, requiring shaving in women, is unacceptable to women who often try new treatments such as laser and depilatory treatment at great expense. (New 2006)

Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH) refers to a family of inherited disorders in which defects occur in one of five enzymatic steps required to synthesize cortisol from cholesterol in the adrenal gland. Because of the impaired cortisol secretion, ACTH levels rise via a negative feedback system
and stimulate adrenal hormone secretion, resulting in hyperplasia of the adrenal cortex. In 21OHD, which is responsible for 90–95% of CAH cases, there is an accumulation of the precursors immediately proximal to the 21-hydroxylation step in the pathway of cortisol synthesis, and these precursors are shunted into the androgen pathway (New 2006)

Non-classic adrenal hyperplasia is most commonly attributable to mutations in CYP21A2 (also termed CYP21) encoding steroid 21-hydroxylase. Partial deficiency of this enzyme causes an imbalance in cortisol synthesis with consequent adrenal androgen excess. Unlike more severe forms of congenital adrenal hyperplasia, this condition is rarely recognized in infants, but rather is a potential cause of premature adrenarche and pubarche in children, virilization in young women, and variable symptoms in young men. (White and Speiser 2000)

**Adrenal Crisis**

A deficiency of 21-hydroxylase causes an inability to synthesize adequate amounts of aldosterone, which is essential for sodium homeostasis. This causes the loss of large amounts of sodium in urine, which leads to potentially fatal electrolyte and water imbalance. Individuals with severe deficiency can present with "adrenal crisis". (White and Speiser 2000)

Although the NC21OHD adrenal crisis is considered theoretical, a recent case report described a patient that was admitted for the treatment of Graves' hyperthyroidism and was later found to be unconscious in the hospital. Thyroid hormones accelerate glucocorticoid turnover, which unmasks Addison's disease or subclinical adrenocortical disease. In this case, thyroxine precipitated an adrenal crisis. (Takasu, Nakachi et al. 2010)

**Autoimmune Adrenal Deficiency**

In autoimmune adrenal deficiency, auto-antibodies target the 21-hydroxylase (21OH) protein. (Rottembourg, Deal et al. 2010) (Bratland, Bredholt et al. 2009)

**Menstrual Disorders**

A recent study found that the prevalence of NCAH in hyper-androgenic women was 2.68%. Their leading symptom was oligomenorrhea. Skin androgenic disorders were a minor clinical problem. None of the NCAH patients had an elevated DHEAS, the androgen dominantly produced by the adrenal glands. (Fanta, Cibula et al. 2008)

**Polycystic Ovary Syndrome**

The clinical symptoms of non-classic adrenal hyperplasia are identical with polycystic ovary syndrome (PCOS). (Fanta, Cibula et al. 2008)
A study was on the prevalence of non-classical congenital adrenal hyperplasia (NC-CAH) due to 21-hydroxylase deficiency among Greek women with hirsutism and polycystic ovary syndrome (PCOS) revealed after ACTH testing, that both reach a rate of 20%. (Trakakis, Rizos et al. 2008)

**Insulin Resistance**

CAH patients are prone to have metabolic disorders in association with elevated serum testosterone levels and reduced insulin insensitivity.

A recent study examined newly diagnosed young adult female patients with simple virilizing 21-hydroxylase deficiency. As compared with the controls, CAH patients had higher BMI (BMI, 21.5 ± 2.1 vs. 20.0 ± 1.8 kg/m(2), P < 0.05), higher 2 hour post-load plasma glucose levels (6. 35 ± 1.74 vs. 5. 35 ± 1.17 mmol/l, P < 0.05), higher serum triglycerides (TG) (1.12 ± 0.64 vs. 0.63 ± 0.15 mmol/l, P < 0.01), and lower high-density lipoprotein cholesterol (HDL-c) (1.30 ± 0.39 vs. 1.67 ± 0.29 mmol/l, P < 0.01). Moreover, CAH patients had higher fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) (1.81 ± 0.99 vs. 1.24 ± 0.50, P < 0.05), while ΔIns30/ΔGlu30 showed no statistically significant difference in two groups. In addition, a marked reduction of serum adiponectin levels were observed in CAH patients (7.0 ± 3.3 vs. 13.2 ± 4.8 µg/ml, P < 0.001), however, serum CRP levels were not different between patients and the controls. (Zhang, Yang et al. 2010)

One study found increased fat mass and higher insulin levels in patients older than 30 years with CAH due to 21-hydroxylase deficiency. (Falhammar, Filipsson et al. 2007)

**Abdominal Obesity in Men**

An older study found that abdominal obesity in men may be associated with decreased activity of adrenal 21-hydroxylase. The study examined prospectively pituitary and adrenal function relative to abdominal obesity defined by waist-to-hip circumference ratio (WHR) in 71 normotensive men aged 30-55 years. In multivariate analyses the ratio of mean ACTH to cortisol, cortisol response to ACTH, and the ratio of net 17-OHP to 11-deoxycortisol increments were all significant predictors of WHR independent of smoking, physical activity, and BMI explaining 49.0% of the variance in WHR. (Hautanen and Adlercreutz 1996)

**Cardiovascular Risk**

Carotid intima-media thickness, a measure of subclinical atherosclerosis, was found to be increased in adults with CAH due to 21-hydroxylase deficiency. (Kim and Merke 2009)
Liver Enzymes

Compared with controls, women with CAH due to 21-hydroxylase deficiency have higher liver function tests (LFT), in particular patients > or =30 years and those with severe forms, probably reflecting a higher lifetime glucocorticoid exposure. LFT were positively correlated to measurements of body fat. (Falhammar, Filipsson et al. 2009)

Acne vulgaris

The frequency of 21-hydroxylase enzyme deficiency in healthy male subjects was 1:43 (2.3%), while in male patients with acne vulgaris, this was 6:43 (13.95%). (Sharquie, Noaimi et al. 2009)

Bone Density

Young adult patients with the classical form of CAH have decreased bone density values, which may put them at risk of developing osteoporosis early in life. (Scianamblo, Russo et al. 2006)

Conventional Lab Tests

An early morning (before 0800) baseline serum 17-OHP by liquid chromatography/tandem mass spectrometry appears to be the screening test of choice in symptomatic individuals after infancy. A screening serum 17-OHP greater than 6 nmol/l or 200 ng/dl warrants obtaining a complete adrenocortical profile following cosyntropin stimulation to differentiate 21-hydroxylase deficiency from other enzyme defects and to make the diagnosis in borderline cases. Menstruating women should be screened in the early follicular phase of the menstrual cycle. (Speiser, Azziz et al. 2010)

17-OHP levels are not specific. One case described a patient who was detected on neonatal screening for 21-hydroxylase deficiency. Further testing, however, revealed 3beta-Hydroxysteroid dehydrogenase type II deficiency, a rare form of congenital adrenal hyperplasia. (Nordenstrom, Forest et al. 2007)

The most definitive hormonal diagnostic test for 21OHD is an ACTH (Cortrosyn 0.25 mg) stimulation test, which measures the serum concentrations of 17-hydroxyprogesterone (17-OHP) at 0 and 60 minutes after ACTH administration. (New 2006)

A recent study found that the aldosterone-to-renin ratio is a marker of disease severity in 21-hydroxylase deficiency congenital adrenal hyperplasia. (Nimkarn, Lin-Su et al. 2007)

Specialty Tests

21-hydroxylase deficiency results in the following changes in steroid hormones:
Increased upstream metabolites: progesterone, 17-OH progesterone, pregnanediol, pregnenolone, etc.

Decreased downstream metabolites: cortisol, cortisone, corticosterone, aldosterone, etc.

The 24-Hour Urine Steroid Hormone Test by Meridian Valley Lab assesses these hormones and many more. Instead of progesterone, it measures pregnanediol, one of its metabolites.

Salivary 17-hydroxyprogesterone and androstenedione assays may be useful as non-invasive tests for home monitoring of hydrocortisone replacement therapy in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. (Wood 2009)

**Conventional Treatments**

Treatment of the classic or severe form of CAH is targeted at replacing cortisol and aldosterone and effectively controlling excess androgen symptoms by using the lowest possible glucocorticoid dose. Treatment of the mild or non-classic form is targeted at controlling excess androgen symptoms and may or may not involve glucocorticoid therapy. Hydrocortisone is the treatment of choice for children. (Merke 2008)

Preliminary studies of the reversal of hyperandrogenic signs in patients with NC21OHD indicate that it took about 3 months of treatment to reverse acne and infertility. The treatment required for this reversal is generally 0.25 mg dexamethasone at the hour of sleep. (New 2006)

**Metformin**

A recent study showed that Metformin (Glucophage), an agent known to reduce insulin resistance, further suppressed the 17-hydroxyprogesterone concentration in a patient with classic congenital adrenal hyperplasia on steroid replacement therapy. Metformin may improve clinical and biochemical outcomes in classic congenital adrenal hyperplasia without the risk of iatrogenic Cushing syndrome. (Mapas-Dimaya, Agdere et al. 2008)

**Natural Therapies**

First described in 1979, NC21OHD is a fairly recently discovered disorder. Although 21-hydroxylase is relatively common, the research on natural therapies is sparse and somewhat discouraging. Both resveratrol and vitamin D have been shown to decrease 21-hydroxylase activity. This research, however, appears to focus on reducing excess cortisol (i.e. mild Cushing’s disease), which is the opposite of what’s needed in 21-hydroxylase deficiency. More research is needed. (New, Lorenzen et al. 1979)
Resveratrol
Phytoestrogen resveratrol suppresses steroidogenesis by rat adrenocortical cells by inhibiting cytochrome P450 c21-hydroxylase. Corticosterone production was inhibited 47% by 50 microM resveratrol in vitro and 20% ex vivo, whereas progesterone production was elevated to 400% of the control value in in vitro experiments. (Supornsilchai, Svechnikov et al. 2005)

Vitamin D3
1alpha,25-dihydroxyvitamin D(3)-mediated a decrease in corticosterone and androgen production due to suppression of the 21-hydroxylase activity by CYP21A2 and the 17,20-lyase activity by CYP17A1, respectively. (Lundqvist, Norlin et al. 2010)

Reducing Cortisol Naturally
Although their effect on 21-hydroxylase was not examined, several dietary supplements have been shown to reduce cortisol. More research is needed on their effect in 21-hydroxylase deficiency.

Vitamin C (Peters, Anderson et al. 2001) (Kodama, Kodama et al. 1994) (Liakakos, Doulas et al. 1975)
Phosphatidylserine (Monteleone, Beinat et al. 1990) (Monteleone, Maj et al. 1992)
Ginkgo biloba (Jezova, Duncko et al. 2002)
Rhodiola rosea (Panossian, Wikman et al. 2010) (Olsson, von Scheele et al. 2009)
Magnolia officinalis and Phellodendron amurense (Garrison and Chambliss 2006)

Adaptogens
An over-simplified view would state that all dietary supplements that reduce cortisol should be contraindicated in 21-hydroxylase deficiency, however, a more thoughtful approach considers the effect of adaptogens.

Adaptogens, such as Rhodiola and Magnolia, help the body adapt to and resist stressful conditions. In acute stress, the body naturally responds by increasing cortisol production. In chronic stress, however, cortisol levels are elevated. In severe stress, the cortisol levels are decreased. One of the criteria for defining an adaptogen is that it has a normalizing influence on physiology, irrespective of the direction of change from physiological norms caused by the stressor. As such, we would expect adaptogens to normalize cortisol levels. (Kelly 2001)
More research is needed on the effects of these supplements on the activity of 21-hydroxylase and their potential use in non-classic 21-OHD.

**Conclusion**

21-hydroxylase deficiency is relatively common and is routinely screened for in newborns, but not adults. The enzyme converts progesterone into deoxycorticosterone and 17-OH progesterone into 11-deoxycortisol. 21-OH deficiency results in increased upstream metabolites (progesterone, 17-OH progesterone, etc.); and decreased downstream metabolites (cortisol, corticosterone, aldosterone, etc.), which causes adrenal hyperplasia. More research is needed in natural therapies for individuals with 21-hydroxylase deficiency.
References


Peters, E. M., R. Anderson, et al. (2001). "Vitamin C supplementation attenuates the increases in circulating cortisol, adrenaline and anti-


