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A recently characterized, underdiagnosed cause of female androgenetic alopecia and polycystic ovarian syndrome: non-classical 21 hydroxylase deficiency

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If you harken back to medical school, to recall the complex steroid pathway controlled by enzymes that catalyze production of various steroid hormones from cholesterol, you may remember the pathologic entity of 21 hydroxylase deficiency—but probably don't expect to see it in your clinical practice. Classical 21 hydroxylase deficiency is genetically inherited and, though it is the most common autosomal recessive disorder, affects only 1:10,000-23,000 live births depending on the ethnicity of the population.[1] Gene mutations can occur and result in only 0-5% of normal 21 hydroxylase enzyme function, which prevents cholesterol from continuing down the path to form cortisol and mineralocorticoid (aldosterone). Instead, there is a buildup of 17 hydroxy progesterone (17-OHP), just prior to the 21 hydroxylase step, and this leads into a pathway causing overproduction of androgen steroids. Affected female babies are virilized prenatally and born with ambiguous genitalia, and when enzyme deficiency is profound, dangerous and sometimes deadly salt wasting occurs, too. The lack of cortisol and, therefore, the lack of its negative feedback results in increased ACTH production and congential adrenal hyperplasia (CAH). What was not recognized until the early 1980s is an entity now known as Non-Classical 21 Hydroxylase Deficiency (NC21OHD). These patients have a decreased production of the 21 hydroxylase enzyme (20-60% of normal), but produce a sufficient amount to reduce or eliminate prenatal virilization (females do not have ambiguous genitalia) and sufficient mineralocorticoid production to avoid salt wasting.[2,3,4] The gene, identified as part of the cytochrome p450 enzyme system and which encodes for 21 hydroxylase, is known as CYP21A2.

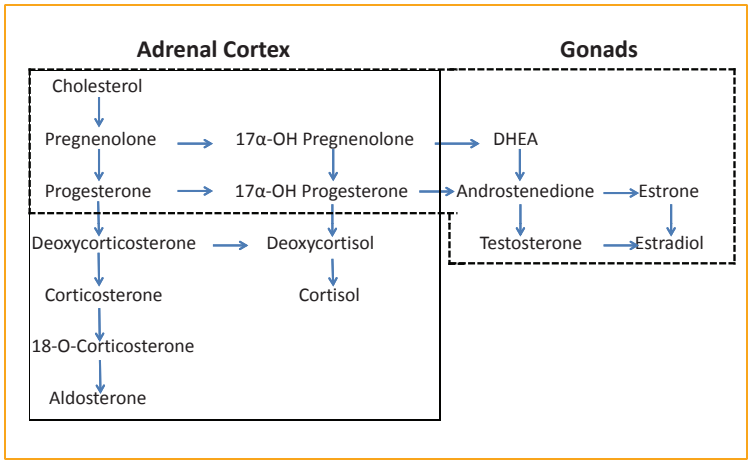

Figure 1. Steroid pathway.

Since the introduction of polymerase chain reaction (PCR) techniques in the 1990s, several mutations in the CYP21A2 gene have been identified that result in variable degrees of enzyme insufficiency, and thus produce a continuum of phenotypes and asymptomatic carriers. In women, symptoms can include cystic acne, hirsutism, hair loss, obesity, decreased fertility, and polycystic ovaries. The most striking finding in recent population surveys is that the frequency of these gene mutations is as high as 10% or more in certain ethnic groups. With such a surprisingly high phenotype prevalence, it is likely we have seen them in our practices.[1] For example, it is estimated that 1:100 people in the city of New York manifest this clinical entity because of their ethnicity.[4]

Critical to appropriate therapy to prevent the symptoms is recognition of the entity's variety of presentations to allow the correct diagnosis. However, laboratory analysis is not always straightforward. This article will present a brief review of the history of molecular characterization, the genetic mutations and population frequencies, and the spectrum of symptoms, as well as recommended methods for diagnosis and difficulties in identifying this entity. Finally, a review of recommended approaches to therapy will be offered because, importantly, early treatment in some patients can effectively ameliorate symptoms of hyperandrogenism such as hirsutism, acne, and fertility issues, and perhaps even hair thinning.

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AGA and POS

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History and Molecular Characterization of NC21OHD

A Nobel Prize was awarded in the 1930s for the contributions of Reichstein and Kendall who first isolated adrenal steroids.[3] Although varying degrees of disease severity for classical 21 hydroxylase deficiency had been recognized, the first report of the distinct clinical entity of NC21OHD was published in 1979, and in 1986 the gene responsible for production of 21 hydroxylase was identified. Since that time PCR techniques have helped identify over 100 genetic mutations impacting the gene to cause both classical and non-classical 21 OH deficiency.[4]

The CYP21A2 gene, as mentioned previously, is a member of the cytochrome P450 (CYP) family and it controls transcription of enzymes that hydroxylate steroid precursors in the adrenal cortex to form corticosteroids and the mineralocorticoids. It is located on Chromosome 6 in the class III region of the major histocompatibility complex (MHC)(6p21), and is near an inactive pseudogene (CYP21P) that contains several inactivating mutations that can be transferred to the active CYP21A2 gene by gene conversion or deletion. Mutations can result in minimal or severe symptoms depending on the degree of the resultant enzyme production deficiency, and asymptomatic patients may be complex heterozygotes. The clinical phenotype in such cases has been observed to correlate well with the less severely mutated allele, resulting in activation of the allele that produces the higher level of 21 hydroxylase.[4,5] Because a divergence between observed phenotype compared to genotype has been observed in some patients, other factors such as the effect of androgen sensitivity related to CAG repeats in the androgen receptor (AR) gene are thought to be potential contributing factors.[5] The number of CAG repeats on the N terminal of the AR gene has been shown to be inversely related to androgen receptor binding, so that smaller numbers of CAG repeats appear to result in a greater sensitivity to androgen hormones.[6] In the case of NC21OHD, a patient who is either more or less sensitive to their androgens would be expected to be more or less sensitive to increases in androgen produced by this condition. It has been speculated that other genetic polymorphisms that influence the quantity and activity of steroid enzymes or hormone response may also be able to influence phenotype variability.[2,5]

Frequency and Prevalence of NC21OHD

The CYP21A2 gene is felt be one of the most highly polymorphic. The estimated incidence of mutations in the population causing NC21OHD is much higher than classical 21-OHD, at 1:500 to as high as 1:100 in various population surveys.[1] As previously noted, certain populations have been found to have a much higher incidence, such as Ashkenazi Jews at 1:27 (1:3 are allele carriers), Hispanics at 1:40, Slavs 1:50, and Italo-Americans at 1:300.[4,15] A recent assessment of the CYP21A2 gene dosage by real-time PCR in 144 individuals randomly sampled from the Spanish population identified that 12% were mutation carriers for NC21OHD.[1] Similarly, in Greece, a random sampling of 494 infants were genotyped, with findings of mutations for NC21OHD in 7.44%.[7] It seems likely we will continue to identify at-risk populations as more and larger gene surveys are performed.

Clinical Features of NC21OHD

First it must be appreciated that not all people with NC21OHD will be symptomatic; for example, symptoms of mild hyperandrogenism are not generally noticed in males. Depending on the degree of enzyme activity, patients may be identified in childhood due to premature pubarche (early findings of body hair: <8 years in females, <9 years in males; apocrine odor) or accelerated linear growth and skeletal maturation, which results in a taller than average child for age, but ultimately shorter adult stature, due to premature closure of epiphyseal growth plates.[2,4] Symptoms in adolescence and adulthood are more likely to identify affected females as they relate to unexpected hyperandrogen symptoms, with the most common being hirsutism, oligomenorrhea, and cystic acne. Decreased fertility has been ascribed to this condition; however, a recent survey showed only 12% of affected women experienced difficulty with fertility, indicating most had normal fertility.[2,4,8] From a hair restoration surgeon's perspective, it is important to be aware of a case report of male pattern baldness in an affected young woman as a sole presenting symptom, and severe androgenetic alopecia (AGA) with marked virilization has been seen in older women.[2] While no published reports specific to the frequency of hair loss or thinning as part of the NC21OHD entity were found, the prevalence of associated gene mutations in women with clinical evidence of hyperandrogenism has ranged from as low as 1% up to 33% depending on the area of the United States or Europe where the survey occurred.[2] Polycystic ovaries have been found in about half of women with NC21OHD, and, furthermore, estimates are that among women with polycystic ovarian syndrome (PCOS) about 10% have NC21OHD.[4] Previous studies have shown a correlation between adrenal androgen excess and ovarian cyst formation, though the exact mechanism for why this occurs is not clear; amplification of FSH receptors, and disruption of cyclical gonadotropin release have been proposed as causal factors.[9]

Diagnosis of NC21OHD

Elevated 17-OHP concentrations are diagnostic in classical 21-OHD, but may be within the normal range for individuals with NC21OHD. Serum cortisol levels are also usually normal,[2,4] and while other androgens such as testosterone and DHEA have been elevated in some surveys, it is also reported that normal basal androgen levels and clinical presentation cannot be used to screen or diagnose,[10,11,12] as DHEA and androstendione may only be elevated with ACTH stimulation.[13] It seems reasonable to expect that androgen hormones would reflect the degree of enzyme insufficiency, where lower levels of 21 hydroxylase enzyme would cause a reduction of cortisol and stimulate more ACTH, which in turn would stimulate more precursors (DHEA, androstenedione) down the androgen path to produce higher levels of androgens. However, no publications or surveys correlating androgen levels with 21-OH enzyme levels have been found to test this supposition. Because symptoms can occur even when basal androgen and 17-OHP levels are within the normal range—and have not been seen to correlate with hirsutism, acne, or alopecia[11]—the acute ACTH stimulation test remains the gold standard to confirm decreased 21 hydroxylase activity. This test involves collection of a baseline blood sample, followed by synthetic ACTH injection with a second sample collected 30-60 minutes later, which reveals a marked elevation

in 17-OHP among NC21OHD patients. Because of the expense associated with genetic testing, and even ACTH stimulation tests, unstimulated AM levels of 17-OHP in the follicular (pre-ovulatory) phase of the menstrual cycle with levels of 170-300ng/dl as a screening tool is recommended. A positive screening test then indicates the need for ACTH stimulation to make the diagnosis. Once a biochemical diagnosis is confirmed, genetic analysis may be helpful in identifying other affected family members or carriers.[1] For the CYP21A2 gene, a panel of 9 common mutations and deletions detects between 80-98% of disease causing alleles in affected individuals and carriers.[14]

Treatment Considerations

Goals of treatment depend on the age of the patient. For adults, treatment goals are focused on symptomatic relief or improving fertility where this is a problem. As hair restoration doctors, we will not likely be evaluating children where the goals of therapy will be to achieve a normal rate of skeletal maturation. If we do see patients with NC21OHD, it will be related to hair loss/thinning, and clues to the diagnosis may include ethnicity and concomitant hirsutism, obesity, history of a diagnosis of PCOS, or cystic acne. Use of anti-androgens (flutamide, cyproterone acetate, or finasteride) may help women with hirsutism and AGA. Among women with NC21OHD, the use of cyproterone acetate compared to hydrocortisone was more effective in treating hirsutism.[2] Other studies have shown that irregular menses and acne can be reversed with glucocorticoids (0.25mg of dexamethasone at night) within 3 months, while hirsutism took 30 months to resolve on this regimen. Cystic acne caused by NC21OHD has been reported to be refractory to antibiotics and retinoic acid therapies.[4] Although infertility apparently afflicts a relatively small percentage of affected patients, glucocorticoid therapy has been shown effective to restore normal fertility and obviate the need for more expensive fertility therapies. This works by restoring normal menstrual cycles. Specific recommendations for hair loss in the various publications were not provided; however, in women with the genetic predisposition to AGA, it seems likely that controlling androgen levels by treating overstimulation of ACTH, and/or providing androgen blockade, would be helpful. The fact that not all female patients with NC21OHD develop hair loss indicates other factors are necessary to make the hyperandrogenism result in hair loss—possibly other genetic factors related to the androgen receptor gene and the polygenic entity of AGA.

Conclusion

Non-classical 21-OHD is a relatively common autosomal recessive disorder that can present at any stage in life, and is asymptomatic in some. The surprisingly high population incidence of this entity, which includes female hair loss as a symptom, should make this diagnosis part of our differential diagnosis. Women with single or multiple symptoms of hyperandrogenism, such as hirsutism, oligomenorrhea, cystic acne, hair loss and/or PCOS, should be screened with a prefollicular, A.M. 17 hydroxy progesterone level. A high index of suspicion or elevated basal level should be followed with an ACTH stimulation test. Referral to an endocrinologist for further evaluation and therapy is indicated.

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