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

Sharon Keene, MD *Tuscon, Arizona, USA* drkeene@hairrestore.com

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.

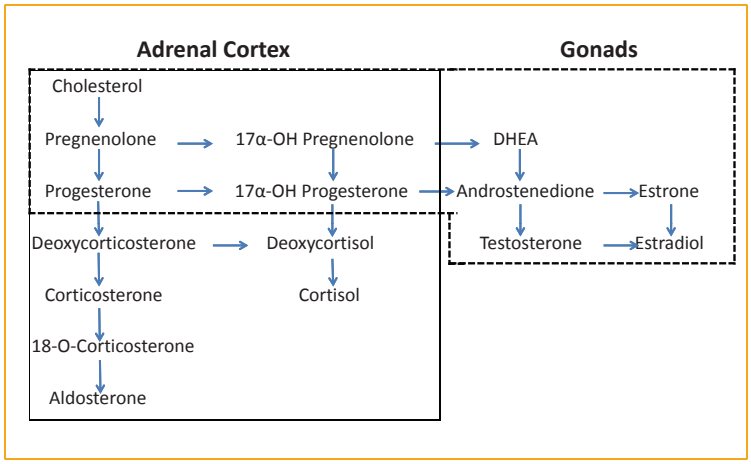

Figure 1. Steroid pathway.

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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