CLINICAL VIGNETTE

Non-Classic Congenital Adrenal Hyperplasia in an Adult Patient

Amy Chow, MD

Case Presentation

A 38-year-old overweight woman presented with worsening hirsutism. For a few years, she noticed hirsutism on the chin, chest, and lower abdomen, which worsened despite multiple laser procedures. Her menstrual period was regular since age 15. She had taken birth control pills from age 17 to 24. She gave birth to a son at age 27, but had difficulty with conceiving her 2nd child. After going through IVF, she gave birth to a daughter at age 33. During infertility evaluation, she was told of a high testosterone level and unknown 17-hydroxyprogesterone without recall of specific levels. Her weight gradually increased over the years.

Her physical exam showed BMI of 28 kg/m^2 with blood pressure and heart rate within normal range. Ferriman-Gallwey (for hirsutism) score[1] was 10 on the exam. The rest of the physical exam was unremarkable. Her laboratory evaluation was significant for 17 alpha-Hydroxyprogesterone 282.55 ng/dl (<=206 ng/dl) at 8am during follicular phase and DHEA-Sulfate 3410 ng/ml (400-3600 ng/ml). NonClassic Congenital Adrenal Hyperplasia (NCCAH) was suspected, and she underwent Cosyntropin stimulation. The post Cosyntropin stimulation 17 -Hydroxyprogesterone level was 1051.15 ng/dl. Because the level was between 1000 ng/dl to 1500 ng/dl, she proceeded with genetic testing for Congenital Adrenal Hyperplasia which was positive for CYP21A2 gene mutation (P453S mutation) and she was referred for genetic counseling.

Discussion

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders. They are characterized by impaired cortisol synthesis due to mutation in CYP21A2, the gene encoding adrenal steroid 21-hydroxylase.[2] This enzyme converts 17 hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycorticosterone, which are precursors for cortisol and aldosterone. The blockage of cortisol synthesis leads to corticotropin stimulation of the adrenal cortex, with accumulation of cortisol precursors that are diverted to sex hormone biosynthesis.[3]

There are different forms of CAH. The most severely affected individuals with classic CAH present during the neonatal periods with adrenal insufficiency, salt wasting and ambiguous genitalia in females.[3]

Non-classic CAH (NCCAH) is a less severe form of the disorder, which features variable degrees of androgen excess but is sometimes asymptomatic.[4] NCCAH is one of the most common autosomal recessive diseases. NCCAH was estimated to have a prevalence of 1:500 to 1:1000 in the caucasian population but up to 1:50 to 1:100 among populations with high rates of consanguineous marriages.[5] More recent CYP21A2 genotype analysis indicates that NCCAH has an overall frequency of 1:200 in the US population.[6]

NCCAH presents later in life with signs of androgen excess. The mild subclinical impairment of cortisol synthesis in NCCAH generally does not lead to Addisonian crises and affected females do not have ambiguous genitalia.[7] Clinical features in late childhood include premature pubarche, acne, and accelerated bone age. Adolescent and adult females present with hirsutism (60 percent), oligomenorrhea (54 percent), and acne (33 percent).[7] About two-thirds of patients carry a severe mutation and patients pursuing fertility should consider genotyping.[3]

Unlike patients with classic 21-hydroxylase deficiency, who are identified either through neonatal screening by detecting very high levels of 17 –hydroxyprogesterone or by clinical findings, most patients with NCCAH will not be identified by neonatal screenings. It is important to consider this condition in adults with typical clinical features of the disorder. Because the clinical presentation of NCCAH can be indistinguishable from that of polycystic ovarian syndrome (PCOS), Endocrine society guidelines recommend measuring basal 17-Hydroxyprogesterone in all women who present with possible PCOS including high-risk group populations like Mediterranean, Hispanic and Ashkenazi Jewish women.[3] Our patient presented with possible PCOS. She had high 17-OH progesterone during the follicular phase of her cycle which led to the diagnosis of NCCAH.

Endocrine Society guidelines, strongly suggest the diagnosis of NCCAH in adult women with basal 17-hydroxyprogesterone values greater than 200 ng/dL (6 nmol/L), confirmed with an ACTH stimulation test. For initial screening, a morning (7:30 to 8 AM) serum sample for 17-hydroxyprogesterone concentration should be obtained during the follicular phase of the menstrual cycle if the woman is cycling regularly. For women with amenorrhea or infrequent menses, the sample can be drawn on a random day.[3] If the basal sample is >200 ng/dL

(6 nmol/L), a high-dose (250 mcg) ACTH stimulation test is suggested, the gold standard for diagnosis. The response to ACTH is exaggerated in NCCAH, and a serum 17-hydroxyprogesterone value exceeding 1500 ng/dL (43 nmol/L) confirms the diagnosis. Rarely, stimulated values at 60 minutes in affected patients range between 1000 ng/dL (30 nmol/L) and 1500 ng/dL (43 nmol/L). This range is inconclusive, and the diagnosis should be confirmed with genotyping of the CYP21A2 gene.[3] The biochemical criteria used for diagnosis in men are the same as those used for women. Adult men are typically asymptomatic but may be diagnosed during a family evaluation. Beyond infancy, there are no age-related differences in the diagnosis of NCCAH based upon high-dose (250 mcg) ACTH stimulation testing. Genetic testing is currently not the primary diagnostic tool for NCCAH. However, it may be used when biochemical results are borderline or when genetic counseling is needed prior to conception.[3]

Combined estrogen-progestin oral contraceptive (OC) is the first-line therapy for hyperandrogenic symptoms and management of oligomenorrhea.[7] Antiandrogens like Spironolactone can be added if the response to OCs is inadequate.[7] Glucocorticoid therapy should only be used for those who do not respond to or cannot tolerate OC and antiandrogen therapies.[7] Stress doses of glucocorticoids are not required for patients with NCCAH unless they have been receiving glucocorticoid therapy, which could suppress their hypothalamic-pituitary-adrenal axis.

Standards have not been established for monitoring glucocorticoid therapy in adults with NCCAH. Concentrations of 17-hydroxyprogesterone, androstenedione, and testosterone should be measured in women, with the goal of normalizing androstenedione and testosterone levels. Adrenal androgen secretion should not be completely suppressed. Suppressed levels of 17-hydroxyprogesterone generally indicate overtreatment, and elevation of 17-hydroxyprogesterone to two or three times the upper limit of normal is acceptable.[7]

Conclusion

Hyperandrogenism like hirsutism can be a presentation of NCCAH. When evaluating a patient with those symptoms, it is important to remember NCCAH as part of differential diagnosis and evaluation.

REFERENCES

1. **Ferriman D, Gallwey JD**. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*. 1961 Nov;21:1440-7. doi: 10.1210/jcem-21-11-1440. PMID: 13892577.
2. **Krone N, Dhir V, Ivison HE, Arlt W**. Congenital adrenal hyperplasia and P450 oxidoreductase deficiency. *Clin Endocrinol (Oxf)*. 2007 Feb;66(2):162-72. doi: 10.1111/j.1365-2265.2006.02740.x. PMID: 17223983.
3. **Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC**. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018 Nov 1;103(11): 4043-4088. doi: 10.1210/jc.2018-01865. Erratum in: *J Clin Endocrinol Metab*. 2019 Jan 1;104(1):39-40. PMID: 30272171; PMCID: PMC6456929.
4. **Kohn B, Levine LS, Pollack MS, Pang S, Lorenzen F, Levy D, Lerner AJ, Rondanini GF, Dupont B, New MI**. Late-onset steroid 21-hydroxylase deficiency: a variant of classical congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 1982 Nov;55(5):817-27. doi: 10.1210/jcem-55-5-817. PMID: 6288753.
5. **Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A, New MI**. High frequency of nonclassical steroid 21-hydroxylase deficiency. *Am J Hum Genet*. 1985 Jul;37(4):650-67. PMID: 9556656; PMCID: PMC1684620.
6. **Hannah-Shmouni F, Morissette R, Sinaii N, Elman M, Prezant TR, Chen W, Pulver A, Merke DP**. Revisiting the prevalence of nonclassic congenital adrenal hyperplasia in US Ashkenazi Jews and Caucasians. *Genet Med*. 2017 Nov;19(11):1276-1279. doi: 10.1038/gim.2017.46. Epub 2017 May 25. PMID: 28541281; PMCID: PMC5675788.
7. **Nieman LK, Merke DP, Lacroix A et al**. Diagnosis and Treatment of NonClassic (late-onset) Congenital Adrenal Hyperplasia due to 21 Hydroxylase Deficiency. In: *UpToDate*, Post, TW (Ed), UpToDate, Waltham, MA, 2022.