



Severe Hirsutism in Non-classic Congenital Adrenal Hyperplasia: A Case Report and Literature Review

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Abstract

BACKGROUND: Non-classic congenital adrenal hyperplasia (NCAH) is a relatively common disorder, but very often, it remains undiagnosed. Clinical appearance of NCAH can be asymptomatic at birth. Symptoms are presented more often in late childhood, adolescence, or later in life caused by excessive androgen secretion.

CASE REPORT: We report the case of 27-year-old girl with 2 years history of high-grade of hirsutism, hair loss on the front of scalp with female pattern hair loss, (grade II according to Ludwig scale), breast volume reduction, weight loss (15 kg), depression, but without menstrual disorders, normal blood pressure, and usage of oral contraceptives for more than 1 year without any improvement. We did blood tests for hormonal protocol for hyperandrogenemia and we found these values high 17 (OH) progesterone and all other androgen hormones. After these examinations, the patient was diagnosed with a non-classic form of CAH.

CONCLUSION: Treatment with corticosteroids and other necessary treatment improved clinical and hormonal features.

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive disorders that affect adrenal glands, characterized by impaired cortisol synthesis and adrenal androgen excess caused by a deficiency in one of the enzymes necessary for the synthesis of cortisol, aldosterone, or both of them. CAH is mostly caused by CYP21A2 mutations, the gene responsible for 21 hydroxylase enzyme synthesis, and precursor for cortisol and aldosterone [1], [2]. Depending on the deficiency of enzyme, the CAH can be classic (complete or almost complete enzyme deficiency) or non-classic or mild form (some enzyme activity is retained) [3], [4]. Due to the CYP21A2 deficiency or 21 hydroxylase enzyme, the defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol results in decreased cortisol synthesis and therefore increased adrenocorticotropin hormone (ACTH) secretion that stimulates the adrenal cortex to accumulate cortisol precursors that are diverted into excessive androgens

production, responsible for symptoms of non-classic CAH. In patients with the non-classic CAH, although enzymatic activity is reduced, it is sufficient to keep up normal glucocorticoid and mineralocorticoid production at the expense of excessive androgen production.

Classic CAH can be salt-wasting or simple virilizing type. The incidence of CAH ranges from 1:10000 to 1:20000 births [5], [6]. The non-classic CAH disease is mild and usually can be asymptomatic at birth [7]; symptoms are presented more often in late childhood, adolescence, or later in life caused by excessive androgen secretion [8]. Non-classic CAH from 21-OH deficiency is much more common than classic CAH [9], with a reported prevalence of 0.1–0.4% in the general population [10]. It is also more frequent in certain ethnicities such as a Mediterranean, Middle-Eastern Ashkenazi Jewish, and Indian population [11]. Around 95% of non-classic CAH are due to 21-OH deficiency [12].

We present a patient with severe clinical signs of hyperandrogenism.

Case Report

A 27-year-old Caucasian woman came to the hospital in the winter of 2016 with a 2 years history of increased hair growth of face (Figure 1), chest, lower abdomen, lower spine, arm and legs with a high scale of hirsutism, without menstrual disorders and clitoromegaly, hair loss, breast volume reduction, weight loss (15 kg), and depression in admission. Facial hair growth required shaving 2–3 times/week. She used to take oral contraceptives (OCs) for more than 1 year without any clinical improvement.

In physical examination, she had heart rate 80/min, blood pressure 120/80 mmHg, and hirsutism was evaluated based on Ferriman–Gallwey score which resulted very high (result = 23). Hair loss was centered in the frontal region of the scalp (male pattern hair loss grade II according to Ludwig scale), (Figures 2). In the ultrasound, ovaries were without cystic changes. Magnetic resonance imaging of abdomen showed slightly hyperplasia of both adrenal glands without any other changes in abdominal organs. In laboratory analyses, total testosterone was 93 ng/dL (<75), dehydroepiandrosterone sulfate (DHEA-S) 639.9 pg/mL (35–430 pg/ml), 17- hydroxyprogesterone 6.59 nmol/L (0.1–0.8), androstenedione 10 ng/mL (0.4–3.4), ACTH 79.7 pg/ml (5.0–46.0), cortisol 553.6 nmol/L (138.0–690.0), prolactin 20 ng/mL (0–20), and luteinizing hormone/follicle-stimulating hormone 2.1 (>2.5 positive for polycystic ovarian syndrome [PCOS]). It was not possible to be realized genetic testing in our country but based on clinical and laboratory analyses, the diagnosis of non-classic CAH was made.

Dexamethasone 0.25 mg once daily was started in midnight for 1 month following 0.5 mg for next 2 months and spironolactone 50 mg twice a day. All signs of hirsutism were absent (hirsutism according to Ferriman–Gallwey score after treatment resulted 0) and androgenic hormones were improved (Table 1) after 3 months of treatment (Figures 1 and 2). The patient continues to be treated at lower doses of both drugs in continuation. Periodically potassium analyses were done which always was in normal values. All the patient's photos used in the presentation are with the patient's permission and written informed consent was done.



Figure 1: Hirsutism in face areas in admission and after the treatment

Discussion

We present a patient with a high score of hirsutism, hair loss, and high level of androgenic hormones. Usually, patients with non-classic CAH often have clinical manifestations of hyperandrogenism such as early pubarche, acne, hirsutism, or oligomenorrhoea/amenorrhoea. Female adolescents may present with signs of hyperandrogenism such as acne, hirsutism, and alopecia. Alopecia in women with CAH is of the male pattern type of hair loss [13].

It is known that a basal, morning serum 17-hydroxyprogesterone value (drawn in the early follicular phase in cycling women) greater than 200 ng/dL (6 nmol/L) strongly suggests the diagnosis. Although confirmation of the diagnosis is needed, 250 mg of cosyntropin i.v. is suggested to do [14]. In our patients, 17(OH) progesterone was sufficiently for starting the treatment for non-classic CAH (NCAH).

During the diagnosis, it has to be excluded the most common form of androgen excess as is PCOS.

Table 1: The level of hormones before and after the treatment

Hormones	In admission	3 months after the treatment	Reference values
17 (OH) progesterone	6.59	0.80	0.1–0.8 nmol/L follicular phase
Androstenedione	10	2.2	Female 0.40–3.40 ng/mL
Testosterone	93.0	22.6	<75 ng/dL
DHEA-S	639.9	145.3	35.0–430.0 pg/mL
ACTH	79.7	38.0	5.0–46.0 pg/mL
Cortisol	553.6	23.4	138.0–690.0 nmol/L

ACTH: Adrenocorticotropin hormone, DHEA-S: Dehydroepiandrosterone sulfate.

The origin of hyperandrogenemia in women may be from an ovarian or adrenal source. DHEA-S, DHEA, androstenedione, testosterone, and dihydrotestosterone are the major circulating androgens in women. DHEA is produced 50% in the adrenal gland, 30% from conversion of DHEA-S, and 20% in the ovary. Whereas, both glands equally produce androstenedione



Figure 2: Hair in admission, after 3 and 12 months of the treatment

and testosterone in the adrenal gland (25%), in the ovaries (25%), and 50% from androstenedione conversion [15]. Dihydrotestosterone is classically an intracellular androgen. In this case, DHEA-S along with testosterone was elevated. Our patient had all three of them.

Another important analysis for the diagnosis is a molecular genetic analysis which enables confirmation of the diagnosis and predicting treatment progress except the level of 17 (OH) progesterone. ACTH (cosyntropin) stimulation test continues to be considered as gold standard for distinguishing 21-hydroxylase deficiency from other enzyme defects [13].

Treatment with glucocorticoids is essential since one-third of patients with NCAH have partial cortisol insufficiency [16]. Antiandrogenic drugs like spironolactone might be useful as additional therapy but with it has to be aware of their potential teratogenicity, and they usually are accompanied with OCs. It is recommended regular clinical monitoring of glucocorticoid treatment to avoid long-term complications such as insulin resistance, hypertension, obesity, osteoporosis, fractures, and secondary cortisol insufficiency [17]. As in our case, although not for a long time, almost 3 years in the treatment, none of the complications are present, and she is living a normal life.

Conclusions

In the undeveloped and developing countries where more sophisticated genetic examination are missing or even gold standard like synacthen test is not often available, 17(OH) progesterone analyses are sufficient to start the treatment for NCAH.

Patients with NCAH with a severe level of hirsutism for a short period of time from starting the treatment can reach an excellent response shown in clinical and laboratory data.

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References

- Krone N, Dhir V, Ivison HE, Arlt W. Congenital adrenal hyperplasia and P450 oxidoreductase deficiency. *Clin Endocrinol (Oxf)*. 2007;66(2):162-72. <https://doi.org/10.1111/j.1365-2265.2006.02740.x>
PMid:17223983
- White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev*. 2000;21(5):245-91. <https://doi.org/10.1210/edrv.21.3.0398>
PMid:10857554
- New MI. Extensive clinical experience: Nonclassical 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2006;91(11):4205-14.
PMid:16912124
- Speiser PW. Nonclassic adrenal hyperplasia. *Rev Endocr Metab Disord*. 2009;10(1):77-82. <https://doi.org/10.1007/s11154-008-9097-x>
PMid:18690539
- Pang S, Shook MK. Current status of neonatal screening for congenital adrenal hyperplasia. *Curr Opin Pediatr*. 1997;9(4):419-23.
PMid:9300201
- Therrell BL. Newborn screening for congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am*. 2001;30(1):15-30.
PMid:11344933
- van der Kamp HJ, Wit JM. Neonatal screening for congenital adrenal hyperplasia. *Eur J Endocrinol*. 2004;151 Suppl 3:U71-5. <https://doi.org/10.1530/eje.0.151u071>
PMid:15554889
- Unluhizarci K, Kula M, Dundar M, Tanriverdi F, Israel S, Colak R, *et al*. The prevalence of non-classic adrenal hyperplasia among Turkish women with hyperandrogenism. *Gynecol Endocrinol*. 2010;26(2):139-43. <https://doi.org/10.3109/09513590903215466>
PMid:19718570
- Witchel SF. Nonclassic congenital adrenal hyperplasia. *Curr Opin Endocrinol Diabetes Obes*. 2012;19(3):151-8.
PMid:22499220
- Lekarev O, New MI. Adrenal disease in pregnancy. *Best Pract Res Clin Endocrinol Metab*. 2011;25(6):959-73.
PMid:22115169
- Pinkas H, Fuchs S, Klipper-Aurbach Y, Zvulunov A, Raanani H, Mimouni G, *et al*. Non-classical 21-hydroxylase deficiency: Prevalence in males with unexplained abnormal sperm analysis. *Fertil Steril*. 2010;93(6):1887-91. <https://doi.org/10.1016/j.fertnstert.2008.12.037>
PMid:19200987
- Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *Lancet*. 2005;365(9477):2125-36.
PMid:15964450
- Moran C, Azziz R, Carmina E, Dewailly D, Fruzzetti F, Ibañez L, *et al*. 21-Hydroxylase-deficient nonclassic adrenal hyperplasia is a progressive disorder: A multicenter study. *Am J Obstet Gynecol*. 2000;183(6):1468-74. <https://doi.org/10.1067/mob.2000.108020>
PMid:11120512
- Witchel SF, Azziz R. Nonclassic congenital adrenal hyperplasia. *Int J Pediatr Endocrinol*. 2010;2010:625105. <https://doi.org/10.1186/1687-9856-2010-625105>
PMid:20671993
- Burger HG. Androgen production in women. *Fertil Steril*. 2002;77 Suppl 4:S3-5.
PMid:12007895
- Bidet M, Bellanné-Chantelot C, Galand-Portier MB, Tardy V, Billaud L, Laborde K, *et al*. Clinical and molecular characterization of a cohort of 161 unrelated women with nonclassical congenital

adrenal hyperplasia due to 21-hydroxylase deficiency and 330 family members. *J Clin Endocrinol Metab.* 2009;94(5):1570-8. <https://doi.org/10.1210/jc.2008-1582>
PMid:19208730

17. Nordenstrom A, Falhammar H. Management of endocrine disease: Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. *Eur J Endocrinol.* 2019;180(3):R127-45. <https://doi.org/10.1530/eje-18-0712>