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A HOMOZYGOUS MUTATION c.518T>A (p.Ile173Asn) OF THE CYP21A2 GENE PRESENTING AS NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA (NCAH)



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INTRODUCTION

Congenital adrenal hyperplasia due to P450c21 (21-hydroxylase) deficiency is an autosomal recessive disorder presenting as 3 phenotypes dependent on the residual enzyme activity: two classical ones (salt wasting and simple virilising, SV) and the milder non-classical CAH (NCAH). All forms have increased adrenal androgens.

Around 0.1% of Caucasians and up to several percent of certain ethnic groups are affected by NCAH. This disorder was first described in 1957 by Decourt et al. Reported prevalence in women with androgen excess range from 0.6% to 9%. Higher prevalence has been reported in Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations.

Most NCAH patients remain undiagnosed. Symptoms of NCAH may develop at any age, but are more typical during late childhood/adolescence.

CLINICAL CASE

20-year-old patient followed since 14 years of age due to hirsutism and overweight.

The girl was born small for her gestational age (35 g.w., BW 1400 g and L 45cm.

At 12 years - menarche, initially with regular periods.

At 15 years - periods started to occur 6-8 times a year with increase in body hair.

Overweight and metabolic syndrome were diagnosed .

Metformin was started at 850 mg/day. Weight decreased with 10%, but hirsutism and irregular menstruation persisted.

Baseline 17-OH-Progesterone (17OHPG) was 8 nmol/l and Dehydrocortisone was added to the therapy.

Over the years, the level of 17OHPG decreased without full normalization (Tabl. 1).

In the last year the patient had regular periods and no further progression of hirsutism.

Tabl. 1

Age	14.5 years	15.0 years	15.5 years	19 years
We (kg)/He (cm)/BMI(kg/m ²)	65/158/ 26.1	60.5/159/ 24.0	58/159/ 23.0	58/159/ 23.0
17-OH-PG ng/ml (0.2 – 1.3)	-	8.0	2.5	1.8
LH mIU/ml (1.1-11.6)	5.5	6.8	8.5	-
FSH mIU/ml (2.8-11.3)	5.5	4.9	5.5	-
Testosterone nmol/l (0-1.38)	1.9	1.8	0.9	-
Treatment	Metformin 850 mg/d	Metformin 850 g/d Dehydrocortisone 2.5 mg/d	Metformin 850 g/d Dehydrocortisone 2.5 mg/d	- Dehydrocortisone 5.0 mg/d

METHODS AND RESULTS

The patient was selected as a candidate for CYP21A2 genotyping based on:

- elevated basal 17OHPG;
- hirsutism;
- menstrual irregularities.

Homozygous missense mutation c.518T>A (p.Ile173Asn), was found (Sanger sequencing of the CYP21A2 gene).

The mutation leads to markedly reduced enzyme activity and has been associated with SV CAH, and more rarely with NCAH clinical presentation.

CONCLUSIONS

The patient contributes to the variability in the genotype-phenotype correlations in CAH. Precise etiological diagnosis was made at 20 yrs of age, with subsequent changes of the therapeutic strategy.

Sequencing of the CYP21A2 gene was established after the introduction of the 17OHPG screening in Bulgaria and seems important also for NCAH.

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