

CASE REPORT**NON-CLASSIC FORM OF
CONGENITAL ADRENAL HYPERPLASIA**

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Summary

Introduction: Congenital adrenal hyperplasia is an autosomal recessive disease caused by gene mutation resulting in 21 α -hydroxylase deficiency and a consequent reduction in adrenal steroidogenesis. The disease could present as classic and non-classic form. The frequency of non-classic form is 0.1% in general population, the most common clinical presentation is premature adrenarche, and the diagnosis is made by determining the concentration of 17-hydroxyprogesterone. The recommended treatment is hydrocortisone with close growth monitoring.

Case report: A 7.5-year-old girl was admitted due to premature puberty, accelerated bone maturation and tall stature. The clinical exam revealed hypertrichosis, normal blood pressure and normal ultrasound of internal reproductive organs. The karyotype was 46 XX, the basal and stimulated levels of 17-hydroxyprogesterone were elevated. Clinical and laboratory regression with stagnation of bone and body growth after starting treatment with hydrocortisone confirmed the diagnosis of non-classic congenital adrenal hyperplasia.

Conclusion: Early diagnosis and therapy provide a better quality of life, reaching the target height in adulthood and avoiding the development of complications.

Key words: non-classic congenital adrenal hyperplasia, 17-hydroxyprogesterone, hydrocortisone, children, hyperandrogenism.



INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive genetic disease with inadequate synthesis of the enzyme 21 α -hydroxylase and a consequent reduction in the production of adrenal steroid hormones. In 90% of cases, it is caused by the mutation of the CYP21A2 gene. According to the clinical picture and the level of residual activity of the enzyme 21 α -hydroxylase, the disease is divided into classic and non-classic forms (1). The non-classic form of congenital adrenal hyperplasia (NCCAH) is characterized by a higher frequency (0.1-0.2%) in general population, a later onset of symptoms, a milder clinical presentation and increased activity of steroidogenesis enzymes compared to the classic form of the disease (2, 3). The non-classic form of the disease is more often diagnosed among women, due to the difficult-to-recognize signs of androgen excess in men (4). The most common mutation detected in NCCAH is p.V281L, which in the Western European population has the highest mutation carrier frequency (7.5%) among Spaniards (5).

The clinical presentation of NCCAH in childhood is premature adrenarche as a result of excess androgens, in adolescence: hirsutism, acne, clitoromegaly, irregular menstrual cycles, oligomenorrhea, tall stature and accelerated growth, and in adulthood: infertility and short stature. Differences in the phenotype of patients depend on their age, sex, and level of residual activity of the missing enzyme. If patients are compound heterozygotes of the classic enzyme mutation, NCCAH is usually detected at an earlier age and is characterized by a more severe clinical presentation (1). NCCAH is rarely diagnosed by neonatal screening due to its failures. If there is suspicion, the level of 17-hydroxyprogesterone (17-OHP) is determined by taking an early morning blood sample or during the follicular phase in girls with the menstrual cycle. Values of 17-OHP concentrations that are up to 2 ng/ml are considered physiological, those from 2-10 ng/ml require an additional ACTH stimulation test, and all values higher than 10 ng/ml are sufficient for the diagnosis of CAH (6). In NCCAH, basal values of 17-OHP are often elevated to more than 15 nmol/L (5 ng/ml), while values below 6 nmol/l (<2 ng/ml) generally rule out NCCAH. A stimulated value, after the ACTH stimulation test, above 30 nmol/l (>10 ng/ml) is sufficient for the diagnosis of NCCAH. The dilemmas surrounding the

value of 17-OHP could be resolved by genetic testing (6, 1). Patients with NCCAH generally have adequate basal cortisol reserves and therefore do not require increasing the hydrocortisone dose in stressful situations, compared to the classical form of the disease. Determining the concentration of cortisol is not necessary for the diagnosis of NCCAH. Its diminished response could be detected by the ACTH stimulation test, when its concentration is lower than 18 μ g/dl 60 minutes later (7).

Unlike the classic form of the disease, the decision to treat NCCAH is mainly reserved for symptomatic patients who present with hyperandrogenism. Glucocorticoid therapy in the pediatric age is limited to hydrocortisone (10-15 mg/m²) due to its diminished negative impact on growth. The use of hydrocortisone preparations with extended release and continuous intravenous subcutaneous infusions have been described in literature. Mineralocorticoid therapy, such as fludrocortisone is rarely used in NCCAH, except for reducing the administered dose of glucocorticoids (1).

CASE PRESENTATION

A 7.5-year-old girl was examined at the Department of endocrinology of the University Children's Hospital in Belgrade due to premature pubic hair, accelerated bone maturation and tall stature. The history revealed that she is the second child from the second uneventful pregnancy, born at term, by Caesarean section. Birth measurements are 3500g/50cm/9, she had regular psychomotor development, no complaints, menarche absent. In the family history, the mother (body height–BH 163 cm) is obese, the father (BH 185 cm) is healthy. On examination, the girl is tall (BH 141 cm; SDS +3.21; P >99), with high growth velocity (high velocity-HV 6.43 cm/yr.; SDS +0.75; P 77.47), obese (BMI 20.37; SDS +1.92; P >97), increased hair on the extremities, normal blood pressure (BP), Tanner staging A (axillary hair) 1, B (breast size) 1, Ph (pubic hair) 3, without clitoral enlargement, the rest of physical exam was unremarkable, **Table 1**.

Diagnostic procedures included measuring the basal values of 17-OHP, which were elevated, so ACTH stimulation test was performed (corticotropin in a dose of 0.25 mg), while the basal values of cortisol, estradiol, testosterone, FSH, LH were in the physiological range for the age (8), which is shown in **Table 2**.

Table 1. Auxological characteristics

	BW (kg)	BH (cm)	HV (cm/yr)	BMI (kg/m ²)	BS (m ²)	TH (cm)	BP (s) mmHg	BP (d) mmHg
	40.5	141	6.43	20.37	1.25	167.5	100	60
SDS	2.71	3.21	0.75	1.92	/	0.61	/	/
P	> 97	99.93	77.47	97.22	/	73.06	40	46

BW-body weight; **BH**-body height; **HV**-High Velocity; **BMI**-body mass index; **BS**- body surface; **TH**-target height; **BP (s)**-systolic blood pressure; **BP (d)**-diastolic blood pressure; **SDS**-standard deviation; **P**-percentile

Table 2. Hormone values

hormone	17OHP (ng/ml)	S 17OHP 30 min	S 17OHP 60 min	C (0 8 h) (ug/dl)	S C (ug/dl)	estradiol (pmol/L)	T (nmol/L)	FSH (U/L)	LH (U/L)
patient values	11.7	18.9	22.3	12.6	15.2	142.5	0.7	1.5	0
normal values (7,8)	< 2	<10	<10	5-23	<18	26-220	0.52-1.21	1.5-12.8	0.10-12.0

17-OHP-17-hydroxyprogesterone; **S 17OHP**- stimulated 17-hydroxyprogesterone; **C**-cortisol; **SC**-stimulated cortisol; **T**-testosterone; **FSH**-follicle-stimulating hormone; **LH**-luteinizing hormone.

Abdominal ultrasound visualized normal internal female reproductive organs, without significant enlargement of the adrenal glands. Bone age corresponded to the age of 11 years and showed advanced bone maturation of +3.5 years (11 years - 7.5 years = 3.5 years). Karyotype is normal female, 46XX.

Based on the clinical picture, anthropometric parameters (BH+3SDS), hormone concentration (increased basal and stimulated 17-OHP), accelerated bone age in relation to chronological age (+3.5 years), it was concluded that the girl had NCCAH. Hydrocortisone treatment was started orally in the dose of 10+10 mg per day, 16 mg/m². The observed response to therapy after five months was the regression of metabolic and clinical parameters. Basal values of 17-OHP (11.7 ng/ml to 6.54 ng/ml) and growth rate (6.43 cm/y to 2.54 cm/y) were reduced, and further bone acceleration was ceased at 11 years. Due to a significant increase in BW (+10kg), which caused a change in body surface area, further correction of the administered dose of hydrocortisone was required, with the continuation of the comparison of metabolic parameters.

DISCUSSION

The classic form of CAH with complete or partial enzyme activity results in a more severe clinical presentation due to cortisol deficiency and androgen excess. The non-classic form of CAH is characterized by 20-70% enzyme activity, which results in mild cortisol deficiency and reduced feedback inhibition of the pituitary gland. The consequence is increased synthesis of ACTH and enlargement of the adrenal gland, which is visualized by ultrasound examination of the abdomen. Partial inactivity of the enzyme 21 α -hydroxylase causes the accumulation of metabolic precursors above the site of its activity, which results in elevated concentrations of 17-OHP, the level of which is determined in diagnostics (1). Neonatal screening rarely detects NCCAH, as concentrations of 17-OHP during the first two weeks are in the physiological range, and their increase occurs only after this

period with no possibility of detecting these patients at that stage (9). In the earliest years of childhood, an excess amount of androgens has no effect on growth rate, but later in childhood their effect becomes apparent. Higher concentrations of androgens and 17-OHP are converted to estrogen, which causes an advance in bone maturity with consequent accelerated pubertal growth. A radiological image of the left hand in children is a gold standard for the estimation of the acceleration of bone maturation in relation to the chronological age. Premature fusion of the epiphyses stops the further growth of the child, and without therapy patients are at risk of not reaching the target height of their parents. Long-term complications of NCCAH include cardiovascular diseases, insulin resistance, obesity, hypertension, diabetes, and psychiatric diseases (1).

Tumors that produce androgens, different exposure to androgens, premature adrenarche or cortisone reductase enzyme deficiency should be considered in differential diagnosis (10).

Treatment aims to suppress accelerated pubertal growth, with minimal risks that the therapy itself carries. In order to avoid possible complications, it is advised to monitor the following: anthropometric parameters (height, weight), signs of sexual development, bone maturity by radiography of the left hand, as well as the measurement of androgen levels (11). New forms of treatment are focused on gene and cell therapy in order to replace glucocorticoid therapy, which will certainly contribute to a better outcome for the patient (12).

CONCLUSION

In patients with a non-classic form of congenital adrenal hyperplasia, early detection of the disease with adequate therapy enables a better and longer life expectancy, while reaching the target height in adulthood. Avoiding the side effects of therapy and minimizing the accompanying complications of the disease requires adequate and constant supervision by a pediatric endocrinologist.

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NEKLASIČAN OBLIK KONGENITALNE ADRENALNE HIPERPLAZIJE

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Sažetak

Uvod: Kongenitalna adrenalna hiperplazija je autozomno recesivno oboljenje gde mutacija gena najčešće izaziva deficit 21 α -hidroksilaze i posledično smanjenje steroidogeneze nadbubrega. Bolest se deli na klasičnu i neklasičnu formu. Učestalost neklasične forme je 0,1% u opštoj populaciji, kliničku sliku karakteriše prevremena adrenaža, a dijagnoza se postavlja određivanjem koncentracije 17-hidroksiprogesterona. Lečenje dece je hidrokortizonom uz praćenje njegovog negativnog uticaja na rast.

Prikaz slučaja: Devojčica uzrasta 7,5 godina hospitalizovana je zbog prerane pubarhe, ubrzanog koštanog sa-

Ključne reči: neklasična kongenitalna adrenalna hiperplazija, 17-hidroksiprogesteron, hidrokortizon, deca, hiperandrogenizam

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zrevanja i visokog rasta. Uočena je pojačana maljavost ekstremiteta, povišene bazalne i stimulisane vrednosti 17-hidroksiprogesterona, normotenzija, uredan ženski kariotip i ultrazvučni pregled unutrašnjih ženskih reproduktivnih organa. Klinička i laboratorijska regresija uz stagnaciju koštanog i telesnog rasta po započinjanju lečenja hidrokortizonom, navode na dijagnozu neklasične kongenitalne adrenalne hiperplazije.

Zaključak: Rana dijagnoza i terapija omogućavaju kvalitetniji životni vek, dostizanje ciljne visine u odrasloj dobi i izbegavanje razvoja komplikacija.