

Congenital adrenal hyperplasia – natural history of the disease – very late diagnosis in a series of patients.

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OBJECTIVES

Inactivating mutations of *CYP21A2* gene cause deficiency of 21-hydroxylase of various degree, what leads to impaired cortisol synthesis, corticotrophin stimulation and accumulation of cortisol precursors that are diverted to sex hormones. CAH SW is usually diagnosed early in neonatal period due to clinical symptoms of salt loss in both sexes, CAH SV usually in early childhood with symptoms of precocious puberty and growth acceleration. NCCAH symptoms develop usually after puberty.

The aim of our study was to present a series of patients with adult diagnosis of classical CAH in terms of clinical presentation, hormonal tests, adrenal and gonadal imaging as well as genetic findings.

METHODS

Six patients (F=3,M=3) with adult diagnosis of classical CAH were qualified to the analysis. CAH was diagnosed based on serum 17OHP confirmed by urine steroid profile made by GC/MS-SIM. Genetic analysis was made by direct sequencing of *CYP21A2* gene.

Patients characteristics consisted of clinical data, metabolic and hormonal assessment, adrenal CT/MR imaging, testicular ultrasound and semen analysis in men.

RESULTS

Table 1. Characteristics of women with CAH

Diagnosis	SVCAH	SVCAH	SVCAH
Age at diagnosis (yr)	18	65	35
BMI (kg/m ²)	33.6	24.8	20
Height (cm)	150	153	146
HOMA-IR	2.78	2.6	8.30
Co-morbidities	No	No	Liver cirrhosis
Menstrual history	Primary amenorrhoea, Virgo	Primary amenorrhoea, Menopause, Virgo	Primary amenorrhoea, Virgo
F-G score	16	12	4
Genitalia	Clitoromrgaly	Clitoromergaly	Urogenital sinus
Alopecia, Acne	NO	NO	NO
Adrenal gland imaging	Normal	Bilateral adrenal tumors (Right-45x30x37 mm, Left18x14x11mm (20-30 HU)	Right adrenal tumor 85x57x70 mm, unhomogenous, without signal loss in MRI out-of-phase
Testosterone nmol/l (0.29-1.67)	9.9	5.15	27.90
Androstendione ng/ml (0.3-3.5)	14.1	10.59	NA
DHEAS ug/dl (60.9-337)	>1000	187 (9-246)	670 (60.9-337)
17OHP ng/ml	23.9	>20	>20
24 h urine 17-hydroksypreganolone (63-279)	60800	2153.6	24007.9
24 h urine pregnanetriol (179-992)	51910	4306.0	19866.5
24 h urine pregnantriolone (3.5-50)	20040	1298.1	4799.6
Free urine cortisol (15-108)	Not established	30	1031.5
Offspring	No	No	No
Genetic evaluation	I172N/deletion	c.293-13C>G/deletion	c.293-13C>G homozygote
Sexual orientation	Hetero	Hetero	Homo
Cortisol (ug/dl) after 250 ug Synacthen im	0' 11.6 30' 12.87 60' 14.13	0' 14.96 30' 18.59	0' 11.27 30' 14.92 60' 16.08
ACTH (pg/ml) 10-60	1518.8	34.5	200
Treatment	Prednisone Vaginal calibration	GCS stress doses	Right adrenalectomy GCS stress doses

Table 2. Characteristics of men with CAH

Diagnosis	CAH SV	CAH SV	CAH SV
Age at diagnosis (yr)	32	52	44
BMI kg/m ²	29.4	33.6	33.7
Height (cm)	178	164	168
HOMA-IR	2,59	DMt2	2,6
Hypogonadic symptoms	Absent	Slight libido decrease	Slight libido decrease
Testis ultrasound	Normal size Microcalcifications	Decreased size Tart's	Normal
Adrenal imaging	CT-Right adrenal tumor 19 mm - 26 HU MRI-borderline signal drop in out-of-phase	Bilateral adrenal hypertrophy	MRI-Left adrenal tumor 42 mm - borderline signal drop in out-of-phase FDG/PET/CT – increased uptake
Testosterone nmol/l (8,64-29)	8.12	17.22	5.42
Androstendione ng/ml	not analyzed	>10	8.04
DHEA-S ug/dl (160-449)	69.3	1363	276
FSH IU/l (1.5-12.4)	0,81	0,29	1,69
LH IU/l (1.7-8.4)	0,44	<0,1	3,16
Semen analysis	oligozoospermia	azoospermia	oligozoospermia
ACTH pg/ml (10-65)	158.1	241.8	70.5
17-OHP ng/ml (<1,7)	6.53	>20	180.1
Urine 17-hydroksypreganolone ug/24h (72-452)	14444.1	52296.7	23138.8
Urine pregnanetriol ug/24h (189-1737)	19841.8	66298	37242.6
Urine pregnantriolone ug/24h (6-66)	5810.2	115690	20789
Urine free cortisol ug/24h (13-120)	431.7	108	648.3
Offspring	No	1	No
Genetic evaluation	I173N/I173N	I173N/I173N	I173N/I173N
Sexual orientation	Heterosexual	Heterosexual	Heterosexual
Cortisol (ug/dl) after 250 ug Synacthen im	0' 16.61 30' 18.58 60' 18.60	0' 15.25 30' 15.65 60' 17.42	0' 13.06 30' 15.28 60' 15.83
Treatment	Stress doses of GCS	Stress doses of GCS	Stress doses of GCS

CONCLUSIONS

Delayed diagnosis of classical CAH in patients in advanced age is possible. Males with hypogonadotropic hypogonadism, adrenal tumors and short stature should be evaluated towards CAH.

Women with primary amenorrhoea and adrenal tumors should be evaluated towards CAH. The assessment of cortisol reserve is mandatory in case of adrenal incidentaloma, elevated ACTH level and no clinical data for hypercortisolism

