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ORIGINAL ARTICLE

Male pseudohermaphroditism as a cause of secondary hypertension: a case report

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Abstract Seventeen alpha-hydroxylase deficiency (17OHD) syndrome is a rare genetic disorder of steroid biosynthesis causing decreased production of glucocorticoids and sex steroids and increased synthesis of mineralocorticoid precursors. There are only 130 cases reported worldwide with documented severe 17OHD. Here, we describe the clinical, hormonal, and molecular genetic characteristics of a Turkish patient with 17OHD, who presented to our clinic due to high blood pressure. A 29-year-old girl with 46,XY genotype was admitted to our nephrology clinic due to uncontrolled hypertension and hypokalemia. The diagnosis was suspected because of primary amenorrhea, absence of sexual maturation, hypertension, and hypokalemia. Endocrine investigation revealed low basal levels of all steroid hormones which require 17-hydroxylation for biosynthesis. Plasma concentrations of ACTH, FSH, and LH were elevated. Imaging did not reveal uterus or adnexial structures. The patient's hypertension and hypokalemia resolved after glucocorticoid replacement and treatment with potassium-sparing diuretics. 17OHD is a rare form of congenital adrenal hyperplasia in which defects in the biosynthesis of cortisol and sex steroids result in mineralocorticoid excess, hypokalemic hypertension, and sexual abnormalities such as pseudohermaphroditism in males, and sexual infantilism in females. 17OHD should be suspected in patients with hypokalemic hypertension and lack of secondary sexual development so that appropriate therapy can be implemented.

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Introduction

The rare variant of congenital adrenal hyperplasia (CAH) known as 17α-hydroxylase deficiency (17OHD) was first described in the 1960s in patients with sexual infantilism and hypertension. It has also been described to present in the setting of male pseudohermaphroditism [1]. 17OHD is a rare autosomal recessive disorder with an estimated incidence of approximately 1:50,000 individuals [2].

Patients with 17α-hydroxylase/17,20-lyase deficiency have alterations in their CYP17 gene, which encodes the P450C17 enzyme [3]. This enzyme plays a central role in steroidogenesis, being essential for the production of cortisol and sex steroids. Thus, patients with 17OHD have reduced secretion of cortisol, androgens, and estrogen with adrenal and gonadal steroidogenesis impairment. Although patients with 17OHD have decreased cortisol production, they do not have signs or symptoms of adrenal insufficiency due to elevations of corticosterone and glucocorticoids. CAH due to 17OHD is associated with hypertension and an excess of deoxycorticosterone (DOC), which is the second most common naturally occurring mineralocorticoid after aldosterone. DOC excess typically is associated with hypertension, hypokalemia, and renin and aldosterone suppression. Till now, more than 130 cases of 17OHD have been reported [4]. 88% of them presented during puberty with hypokalemic hypertension and infantilism; 8% during fourth and fifth decade and 4% during infancy with hypertension and endocrinopathy. Here, we describe the clinical, hormonal, and molecular genetic characteristics of

a Turkish patient with 17OHD, who presented to our nephrology clinic due to high blood pressure.

Case

A 29-years old patient presented to our clinic due to high blood pressure. The patient had high blood pressure for 20 years and was diagnosed as primary amenorrhea 15 years ago. She was a normal uncomplicated delivery of a phenotypically normal female infant to non-co-sanguineous parents of Turkish origin. On physical examination, the patient had eunicoid body shape (height: 176 cm, weight: 55 kg) and female external genitalia with no secondary sex characteristics (no breast development and no pubic or axillary hair) (Fig. 1). Pulse was 84/min and regular, blood pressure was 190/130 mmHg; cardiac examination was normal. There was grade 2 hypertensive retinopathy on fundus examination.

Laboratory evaluation was as follows; Serum urea 23 mg/dl, creatinine 0.76 mg/dl, sodium 145 mmol/l, potassium 2.3 mmol/l, FSH 117 mlU/ml (*N*: 1.38–13.58), LH 65.6 mlU/ml (*N*: 1.7–8.6) and estradiol <10 pg/ml (*N*: 18–110), cortisol 0.1 mg/dl (*N*: 5–25), ACTH 65 pg/ml (*N*: <50), pregnenolone 4.7 ng/ml (*N*: 0.2–1.4), 17-hydroxyprogesterone 0.6 ng/ml (*N*: 0.61–3.34), deoxycorticosterone (DOC) 4099.96 pg/ml (*N*: 40–200), corticosterone 117 nmol/l (*N*: 0–10), dehydroepiandrosterone-sulfate (DHEA-S) 19.0 μg/dl (*N*: 80–560), free testosterone 0.02 ng/ml (*N*: 5–37), aldosterone 250 pg/ml (*N*: 38–313), and PRA less than 0.15 ng/ml/h (*N*: 1.9–6), urinary vanillylmandelic acid (VMA) 3.6 mg/24 h (*N*: 1–11), metanephrine 132 mcg/24 h (*N*: <350) and normetanephrine 355 mcg/24 h (*N*: <600) (Table 1). There was left ventricular hypertrophy on electrocardiography and echocardiography. Abdominal and pelvic ultrasonography and MRI were normal except an image consistent with a mass, 1.5 cm in diameter, in the right inguinal canal which was thought to be testicle; but no uterus or adnexial structures. Cranial magnetic resonance imaging examination performed due to intermittant diplopia was normal. There was no renal artery stenosis on computerized tomography angiography.

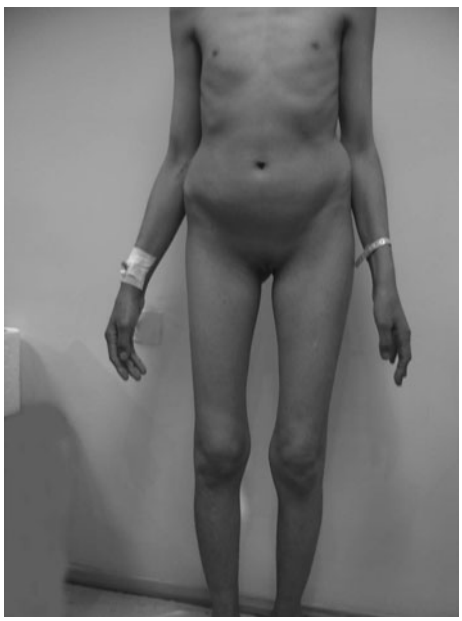

Fig. 1 The patient had eunicoid body shape and female external genitalia with no secondary sex characteristics (no mammarian development and no pubic or axillary hair)

The bone mineral densitometry showed very low bone mineral density with a total T score of −3.8. Chromosomal study showed a karyotype of 46-XY. A diagnosis was made of congenital adrenal hyperplasia secondary to 17OHD in a genotypic male (male pseudohermaphroditism). The treatment protocol of the patient was changed from diltiazem 180 mg/day plus doxazosin 4 mg/day to prednisolon 7.5 mg/day plus spironolacton 100 mg/day. Our patient was referred to the department of gynecology for surgical removal of the inguinal testes. Pathological examination showed testical tissue with no sign of malignancy. Osteoporosis was treated with oral calcium and vitamin D3. We have started transdermal estradiol patch 4 mg twice a week. She is still under follow-up with no complaints and mean blood pressure of 140/85 mmHg.

Discussion

There are a number of causes of secondary hypertension, and specific symptoms and findings may point to a particular disorder. We searched for reasons of secondary hypertension. Renovascular hypertension was excluded because of normal urea and creatinine levels and normal CT angiography of the renal arteries. Aortic coarctation was discarded due to equal blood pressure measurements from both arms and absence of echocardiographic findings. Pheochromocytoma, hyperaldosteronism and Cushing's syndrome were excluded because of normal urinary and serum cathecolamine levels, urinary VMA level, aldosterone, sodium, low basal cortisol levels, and absence of radiologal findings. There was no history of use of drugs and licorice that may cause hypertension. The presence of primary amenorrhea, absence of secondary sex characteristics, and absence of other more common causes of secondary hypertension led us to search for other endocrine causes and measure steroid hormone levels. 11 beta hydroxylase deficiency was excluded due to low DHEA-S and 17 hydroxyprogesterone levels.

Table 1 Laboratory data before glucocorticoid replacement

Variable	Result (before the treatment)	Normal range
Urea	23 mg/dl	0–50
Creatinin	0.76 mg/dl	0.6–1.3
Sodium	145 mmol/l	136–145
Potassium	2.28 mmol/l	3.5–5.5
ACTH	65 pg/ml	<50
Cortisol	0.1 ug/dl	5–25
FSH	117 mIU/ml	1.38–13.58 (M)
LH	50.33 mIU/ml	1.7–8.6 (M)
DOC	12.3 pmol/ml	0.12–0.60
	4099.96 pg/ml	40–200
Corticosterone	117 nmol/l	0–10
	40.95 ng/ml	0–3.5
Aldosterone	250 pg/ml	38–313
Renin	<0.15 ng/ml/h	1.9–6
Progesterone	4.7 ng/ml	0.2–1.4 (M)
Estradiol (E2)	<10 pg/ml	18–110
17-OH PGTR	0.6 ng/ml	0.61–3.34 (M)
Delta androstenedione 1,4	0.02 ng/ml	0.3–2.63 (M)
DHEA-S	19.0 ug/dl	80–560 (M)
Total testosterone	0.36 ng/ml	1.66–8.77 (M)
Free testosterone	0.02 ng/ml	5–37 (M)
VMA (urinary)	3.6 mg/24 h	1–11
Metanephrine (urinary)	132 mcg/24 h	<350
Normetanephrine (urinary)	355 mcg/24 h	<600
Epinephrine (urinary)	3.1 Ug/24 h	2–22
Dopamine (urinary)	395.2 Ug/24 h	40–400
pH	7.51	7.35–7.45
HCO_3	30 mEq/l	22–26

ACTH adrenocorticotropic hormone; *17-OH PGTR* 17-hydroxyprogesterone; *FSH* follicle-stimulating hormone; *LH* luteinizing hormone; *DOC* deoxycorticosterone; *DHEA-S* dehydroepiandrosterone-sulfate; *VMA* vanilylmandelic acid; *M* male

The occurrence of 17OHD is very rare. It is responsible for less than 1% of all cases of congenital adrenal hyperplasia. To date, more than 130 cases of 17OHD and nearly 50 different mutations in CYP17 have been reported [4].

Since 17OHD is an autosomal recessive disease, males and females are affected equally. It is important to note that if karyotypes are not checked, the disease will be detected more often in females than in males, because males with classic 17OHD are phenotypic females [2].

Typically, 17OHD is first recognized in puberty, with the discovery of hypertension, hypokalemia, and hypogonadism [5]. Patients present as phenotypic females, with sexual infantilism and primary amenorrhea, as in our patient. In patients who are 46,XX internal female genitalia are normal but underdeveloped, whereas in patients with 46,XY karyotype the external genitalia are female and corresponding internal müllerian structures (e.g, uterus, fallopian tubes, and ovaries) are lacking due to uninterrupted testicular production of antimüllerian hormone. Patients may have inguinally located testes that may present as inguinal hernias. Secondary sexual characteristics, including axillary and pubic hair, are absent. Breasts are infantile. Less severely affected XY patients may present earlier in life with ambiguous genitalia due to underproduction of androgens. Typically, male patients have been raised as females, with the condition being identified only during puberty, when the expected pubertal changes have not occurred [2, 4]. Patients may be tall, with eunuchoid proportions due to a lack of sex steroids (and thus delayed fusion of epiphysis) [2, 4]. All of these features were found in our patient.

In all variants of 17OHD, the production of sex steroids is absent resulting in a compensatory increase in levels of follicle-stimulating hormone and luteinizing hormone comparable to that in menopause. In humans, the gene product for 17 alpha-hydroxylase (P450C17) is expressed in the adrenal cortex, testes, and ovaries but not in the placenta. The adrenals produce glucocorticoids, mineralocorticoids, and C-19 steroids. The gonads on the other hand, predominantly produce the C-19 steroids and sex hormones. Thus, in

patients with 17OHD, adrenal and gonadal steroidogenesis are impaired [2]. The 17-deoxy steroids, as well as progesterone, corticosterone, and DOC, rise to 5–10 times their normal levels following ACTH stimulation. Elevated progesterone, corticosterone, and DOC levels in the setting of a virtual absence of 17-hydroxyprogesterone, estrogens, and androgens are characteristic of the syndrome. Corticosterone typically is 50- to 100-fold higher than the reference range. Most patients have DOC levels greater than 1000 pg/ml (normal levels being 40–200 pg/dl). The majority of patients (80–90%) present with hypokalemic metabolic alkalosis. Patients have elevated levels of 18-hydroxycorticosterone and 18-hydroxydeoxycorticosterone. Follicle-stimulating hormone and luteinizing hormone levels are markedly elevated, while ACTH levels are marginally elevated [2, 4, 5]. All of these features were found in our patient.

Serum progesterone, which is one of the 17α-hydroxylase substrates and is a useful marker in the diagnosis of 17OHD, was elevated in our patient. The aldosterone levels in most cases are low due to the renin suppression induced by the elevated levels of DOC and other precursor mineralocorticoids [6, 7]. In a previous study, aldosterone levels were found normal in 16 of 125 patients as in our case [8].

Pelvic ultrasonography reveals a lack of müllerian structures in 46,XY patients and demonstrates normal, but underdeveloped müllerian structures in 46,XX patients. The gonads may be intra-abdominal or in the inguinal canal in 46,XY patients. In our case, testes were in the inguinal canal.

Mortality and major morbidities associated with 17OHD stem mainly from delayed recognition or nonrecognition of hypertension. The long-term sequelae of myocardial infarction, cerebrovascular accident, renal failure, heart failure, and peripheral vascular disease may occur if blood pressure is not well controlled. Our patient had grade 2 hypertensive retinopathy on fundus examination and left ventricular hypertrophy on echocardiography. The psychological impact of the hypogonadism and/or ambiguous genitalia associated with the condition may impact the quality of life and social adjustment of patients with 17OHD.

Usually, hypertension resolves with glucocorticoid therapy [9, 10] but it may persist if the diagnosis is delayed. Mineralocorticoid antagonists such as spironolactone or potassium can be added to the regimen to achieve better control of blood pressure. The addition of a calcium channel blocker to the regimen is usually effective if hypertension persists despite adequate blockade of mineralocorticoid production and action [6]. Female sex assignment was continued in this chromosomally male patient due to established psychosexual development and identity. Hormone replacement regimens are best begun early in adolescence to achieve their greatest potential. They allow the development of female secondary sexual characteristics and stimulate the normal increase in bone mass that occurs with puberty. This therapy may also reduce final height [10]. But our patient was already 29 years old, so nothing could be achieved in terms of height.

The testes may be intra-abdominal, in the inguinal canal, or in the labioscrotal folds [2, 10]. Affected 46,XY patients require gonadectomy to prevent malignant degeneration of their gonads. Our patient was referred to the department of gynecology for surgical removal of the inguinal testes. She was not given estrogen replacement because of late referral after adolescense. The treatment was arranged as prednisolone 7.5 mg/day, spironolactone 100 mg/day and diltiazem 180 mg/day.

As a result, in the evaluation of patients with hypogonadism and hypertension, 17-hydroxylase deficiency is an uncommon, but important, consideration. It should be particularly considered in female patients with delayed puberty and low renin hypertension. Adequate psychosocial support is important following diagnosis.

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