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# Congenital Adrenal Hyperplasia as a Cause of Secondary Hypertension in Adults: Three Cases

## Sekonder Hipertansiyon Sebebi Olarak Konjenital Adrenal Hiperplazi: Üç Vaka

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## Abstract

Congenital adrenal hyperplasia is a group of hereditary disorders originating from enzymatic defects in steroidogenesis, resulting in impaired cortisol synthesis in the adrenal cortex. The rare forms of congenital adrenal hyperplasia characterized by hypertension and hypokalemia include 11-β and 17-α hydroxylase deficiencies. We described three cases of congenital adrenal hyperplasia, two with 11-β hydroxylase and one with 17-α hydroxylase deficiency, each presenting with hypertension and hypokalemia in adulthood. In addition, 11-β hydroxylase deficiency cases showed precocious puberty with testicular adrenal rest tumor and adrenal myelolipoma, whereas the patient with 17-α hydroxylase deficiency showed sexual infantilism. Congenital adrenal hyperplasia is a rare cause of secondary hypertension in adults. It is particularly considered in patients with sexual maturation disorders, such as precocious puberty, delayed puberty, or sexual infantilism, and in those with hypertension and hypokalemia.

**Keywords:** Congenital adrenal hyperplasia; secondary hypertension; hypertension; hypokalemia

## Özet

Konjenital adrenal hiperplaziler; adrenal kortekste bozulmuş kortizol senteziyle sonuçlanan enzimatik defektlere sebep olan herediter bir grup hastalıktır. Konjenital adrenal hiperplazilerin hipertansiyon ve hipokalemiye sebep olan nadir formları 11-β hidroksilaz ve 17-α hidroksilaz eksikliği ile gider. Bu çalışmada, hipertansiyon ve hipokalemi ile gelen iki erişkin 11-β hidroksilaz ve bir erişkin 17-α hidroksilaz hastasının sunulması amaçlanmıştır. Prekoks puberte öyküsü olan 11-β hidroksilaz hastalarında, aynı zamanda testiküler adrenal rest tümör ve adrenal miyelolipoma mevcut iken, 17-α hidroksilaz hastamızda da seksüel infantilizim mevcut idi. Konjenital adrenal hiperplaziler erişkinlerde sekonder hipertansiyonun nadir sebeplerindendir. Prekoks puberte, gecikmiş puberte veya seksüel infantilizim gibi seksüel olgunlaşma bozuklukları ve hipertansiyonla birlikte hipokalemi olması durumlarında konjetinal adrenal hiperplaziler akla gelmelidir.

**Anahtar kelimeler:** Konjenital adrenal hiperplazi; sekonder hipertansiyon; hipertansiyon; hipokalemi

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## Introduction

Congenital adrenal hyperplasia (CAH) is a group of hereditary disorders originating from enzymatic defects in steroidogenesis, resulting in impaired cortisol synthesis in the adrenal cortex. The most commonly seen form is 21 hydroxylase deficiency, although this does not lead to hypertension. The rare forms of CAH characterized by hypertension and hypokalemia include 11-β and 17-α hydroxylase deficiency (1).

In addition, 11-β hydroxylase deficiency is the second most common cause of CAH, representing 5% to 8% of cases. It is char-

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acterized by excessive production of adrenal androgens and deoxycorticosterone, leading to virilization (female pseudohermaphroditism) in female fetus and precocious puberty in the male infant. Moreover, excessive androgen production leads to the development of premature and inappropriate secondary sexual characteristics in both sexes. In untreated cases, rapid skeletal growth caused by excessive androgen leads to early epiphyseal maturation and thus to short stature (2).

17-α Hydroxylase deficiency is a rare form of CAH, representing only 1% of all cases. The classic symptoms caused by the lack of the enzyme are hypertension, hypokalemia, and sexual infantilism. Male fetuses with 17-α hydroxylase deficiency possess an external genital structure of female phenotype known as male pseudohermaphroditism. In female fetus, the external genitalia are normal; however, the deficiency causes primary amenorrhea and secondary sexual characteristics do not develop (3).

We describe three cases of CAH, two of 11-β hydroxylase and one of 17-β hydroxylase deficiency, each presenting with hypertension and hypokalemia. In addition, testicular adrenal rest tumor and adrenal myelolipoma were identified in the 11-β hydroxylase deficiency cases.

## Case Reports

Informed consent was taken from all patients.

### Case 1

A 27-year-old man with hypertension presented with flu at the internal diseases' clinic. No abnormality apart from hypokalemia was identified during routine biochemical testing. The patient was started on spironolactone and referred to our clinic. His history revealed that dexamethasone therapy had been initiated following CAH diagnosis at the age of three years when he had presented with pubic pilosity and penile growth. Therapy was stopped at the age of 14 years with the onset of puberty; however, hypertension was not diagnosed.

At examination, he was 158 cm tall and weighed 68 kg. Blood pressure was 200/120 mmHg. Grade 2 hypertensive retinopathy was present in the ocular fundus, and left ventricular hypertrophy was observed by echocardiography. The levels of 17-hydroxyprogesterone, 11-deoxycortisol, and adrenocorticotropic hormone (ACTH) were elevated. Tests were compatible with 11-β hydroxylase deficiency (Table 1). Subrenal magnetic resonance imaging (MRI) revealed bilateral diffuse thickening (Figure 1). Scrotal ultrasonography showed a heterogeneous, solid 5x5 mm lesion in the left testis, containing pronounced central and peripheral venous flows with peripheral calcification. A hypodense nodular area of 10×5 mm in the left scrotal sac was identified in MRI T2 sequences (Figure 2). This was thought to be compatible with testicular rest tumor. The patient refused the biopsy examination of the testicular mass. Spermogram revealed azoospermia.

The patient was started on dexamethasone. Potassium replacement was prescribed as serum potassium levels were considerably low. On follow-up after 3 months, he was normokalemic and normotensive, with no potassium replacement or antihypertensive requirement. Furthermore, we observed a decrease in testicular rest tissue.

### Case 2

A 41-year-old man presented to the emergency department with acute kidney failure associated with gastroenteritis. Left orchiectomy had been performed 6 years ago because of suspected testicular malignity, and histopathological examination reported diffuse coagulation necrosis in the testis. Left adrenalectomy was performed 3 years ago when myelolipoma was diagnosed pathologically. He had azoospermia-associated infertility and was taking eprosartan (600 mg/day) for 5 years for hypertension. His parents were consanguineous, and he was the shortest member of the family (148 cm). Pubic pilosity had begun at approximately 5 years of age and beard growth at approximately 8 years.

The right testis was 30 mL in volume with hard and irregular margins. Grade 1 and 2 hypertensive retinopathy was observed. Left ventricular hypertrophy and an aneurysm in the ascending aorta were identified by echocardiography. At the time of presentation, the patient's potassium level was 4.6 mmol/L, which decreased to 2.8 mmol/L

Table 1. Laboratory characteristics of the cases.

| Laboratory test | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Basal cortisol (μg/dL) | 4.2 | 12.2 | 0.7 |
| Adrenocorticotropic hormone (pg/mL)<br>Normal range: 0-46 pg/mL | 1121 | 117 | 72.6 |
| Dehydroepiandrosterone sulfate (μg/dL)<br>Normal range: 35-430 μg/mL | 351 | 2350 | 0.1 |
| 17-Hydroxy-progesterone (ng/mL)<br>Normal range: 0-1.39 ng/mL | 25 | 31.1 | - |
| Progesterone (ng/mL)<br>Normal range: 0.15-1.4 ng/mL | 7.3 | 28.8 | 9.37 |
| Follicle-stimulating hormone (mIU/L)<br>Normal range: 2.5-10.2 mIU/L | 0.2 | 0.1 | 73.2 |
| Luteinizing hormone (mIU/L)<br>Normal range: 1.9-12.5 mIU/L | 0.1 | 0.1 | 20.2 |
| Free testosterone (ng/mL)<br>Normal range: 8.7-30 ng/mL | 21 | - | - |
| Testosterone (ng/dL)<br>Normal range: 241-827 ng/dL | 274 | 1167 | 0.01 |
| Estradiol (pg/mL)<br>Normal range: 11-69 pg/mL | - | - | 13.1 |
| 11-Deoxycortisol (ng/mL)<br>Normal range: 0-0.5 ng/mL | >100 | 270 | - |
| 11-Deoxycortitestosterone (pmol/mL)<br>Normal range: 0.12-0.60 pmol/mL | - | 18.8 | - |
| Aldosterone (ng/dL)<br>Normal range: 7-30 ng/dL | - | - | 5.7 |
| Renin activity (ng/mL/s)<br>Normal range: 0.70-3.30 ng/mL/s | - | - | 0.15 |

when eprosartan was stopped. 11-β Hydroxylase deficiency-associated CAH was diagnosed on the basis of the clinical and laboratory results (Table 1) and dexamethasone (0.75 mg/day) therapy was started. At the end of the fourth week, the patient was normotensive and normokalemic without antihypertensive therapy and abnormal laboratory values returned to normal.

## Case 3

A 34-year-old woman was referred to our clinic because of hypertension and hypokalemia. She was receiving antihypertensive therapy for the past ten years and had never menstruated. Physical examination revealed no pubic or axillary pilosity, Tanner stage 1 breast development, prepubertal external female genital structures, and a rudimentary vaginal cuff. Laboratory tests showed low levels of cortisol, estradiol, testosterone, and dehydroepiandrosterone sulfate, with high levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), ACTH, and progesterone (Table 1). Bilateral subrenal hyperplasia was noted on abdominal MRI; however, no uterus or

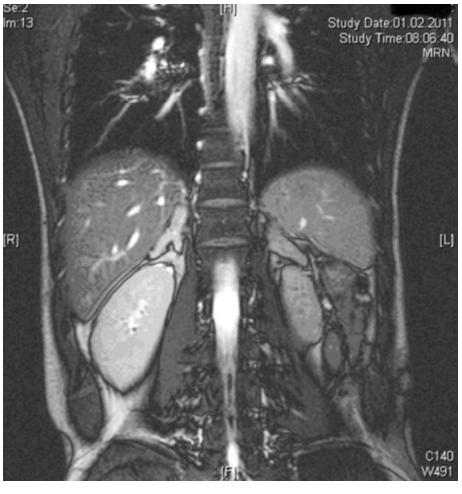


**Figure 1:** Congenital adrenal hyperplasia associated with 11-β hydroxylase deficiency: pronounced bilateral adrenal hyperplasia on a subrenal magnetic resonance image from Case 1.

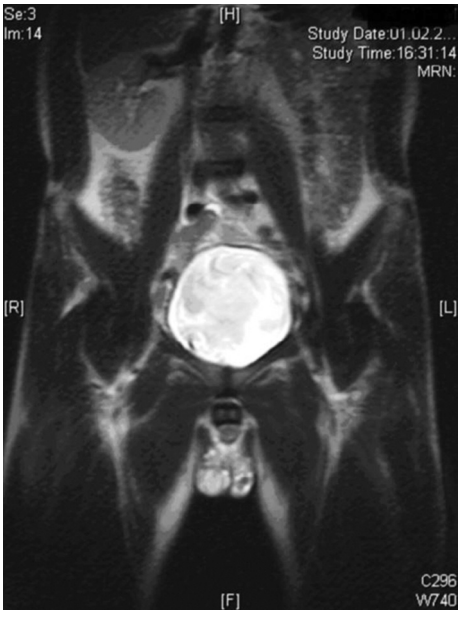


**Figure 2:** Congenital adrenal hyperplasia associated with 11-β hydroxylase deficiency: appearance compatible with hypointense testicular adrenal rest tumor (10x4 mm) in the left testis on a magnetic resonance T2 sequence from Case 1.

ovaries were observed. Karyotype screening was performed and reported 46 XX. The patient's clinical and laboratory findings were compatible with 17-α hydroxylase deficiency, and hypokalemia and hypertension were brought under control with dexamethasone.

## Discussion

Two forms of CAH lead to excessive accumulation of products that induce mineralocorticoid activity. The deficiency of 11-β and 17-α hydroxylase results in excessive production of steroid 21 hydroxylase that activates mineralocorticoid receptors (4). Although hypertension has been reported in children as young as three months old, it cannot generally be reliably determined until late childhood or adolescence (5).

Patients with 11-β hydroxylase deficiency have a set of hormonal findings; high serum concentrations of 11-deoxycortisol, deoxycorticosterone, DHEA, androstenedione, and testosterone, with low cortisol and corticosterone levels (6).

Our first two cases were diagnosed because of hypertension and hypokalemia in addition to precocious puberty and short final height which was associated with 11-β hydroxylase deficiency identified at a relatively later age. Despite insufficient aldosterone production in 11-β hydroxylase deficiency, excessive production of deoxycorticosterone, a less potent mineralocorticoid in vivo, can lead to salt retention and hypertension. Potassium depletion occurs with salt retention; however, hypokalemia is variable. Renin production can be suppressed secondary to sodium retention and volume expansion (2, 6).

In two cases, azoospermia and the appearance compatible with testicular adrenal rest tumor were identified in the testis. The testicular biopsy could not be performed; however, a decrease in mass dimensions after dexamethasone therapy strengthened the diagnosis of adrenal rest tumor. These tumors are believed to originate from the aberrant adrenal tissue descending with the testes in the embryological period. They are commonly seen in association with high ACTH levels in patients with inadequately controlled CAH (7). The mechanical effects of these tumors can lead to obstruction of the seminiferous tubules and ischemic necrosis. Furthermore, the paracrine effects of steroids produced in tumor tissue may have a toxic effect on Leydig and/or germinal cells. In addition to these local effects of testicular adrenal tumors, chronic ACTH elevation secondary to low cortisol production in patients with 11-β hydroxylase deficiency also suppresses the release of FSH and LF, causing excessive accumulation of adrenal androgens. These conditions can lead to decreased testicular size and sperm numbers and male infertility (8).

The second case was suspected of testicular tumor, and necrosis was observed in the testis. In the absence of any histopathological evidence, this condition may have arisen in association with testicular adrenal rest tumor. However, the patient underwent left adrenalectomy, and the histopathological examination of the specimen removed was compatible with adrenal myelolipoma. Myelolipomas are rare benign tumors developing from the hematopoietic elements of the adrenal glands and mature adipose tissue. They are thought to be metaplastic in origin and associated with the chronic stimulation of ACTH and androgens. Myelolipomas are frequently reported in cases of CAH associated with 21 hydroxylase deficiency

(9). One previous case of 11-β hydroxylase deficiency with adrenal myelolipoma has been reported with testicular adrenal rest tumor (10). Early occurrence of 11-β hydroxylase-related CAHs, usually in association with hypertension, probably explains why these tumors are rarely seen (10).

In the third case, the patient with a 46 XX karyotype with primary amenorrhea and sexual infantilism had 17-α hydroxylase deficiency. This enzyme deficiency prevents the synthesis of androgen and cortisol while increasing mineralocorticoid synthesis, leading to hypokalemia and hypertension. Aldosterone levels may be normal or low because of the suppression of renin levels by increasing extracellular volume. Apart from its effects in the adrenal cortex, 17-α hydroxylase deficiency also prevents androgen and estrogen production in the gonads, leading to hypergonadotropic hypogonadism by increasing FSH and LH secretion. Adrenal crises are not typically seen in patients with 17-α hydroxylase deficiency because of increased synthesis of corticosterone with weak cortisol activity (3, 11). The diagnosis of 17-α hydroxylase deficiency is generally based on clinical and laboratory findings and genetic analysis. The plasma levels of progesterone, corticosterone, and deoxycorticosterone acetate are typically five to ten times higher than normal (3). An increased basal progesterone level has recently been described as a suitable marker in 17-α hydroxylase deficiency. Progesterone also increases in 11-β and 21 hydroxylase deficiencies. However, in contrast to 17-α hydroxylase deficiency, these two disorders are the virilizing forms of CAH (12).

Hypertension and hypokalemia were brought under control with dexamethasone therapy in all three patients. Steroid replacement reduces the formation of deoxycorticosterone by reducing ACTH levels and corrects hypertension and hypokalemia in most patients (1). However, in patients with prolonged hypertension before diagnosis, potassium-binding diuretics such as spironolactone and calcium channel blockers such as nifedipine may be required. Angiotensin-converting enzyme inhibitors are ineffective because the renin-angiotensin-aldosterone system is suppressed (1, 13). Blindness, retinal vein occlusion, and cardiomyopathy associated with long-term uncontrolled hypertension have been reported in patients with 11-β hydroxylase deficiency (14, 15).

In conclusion, CAH is a rare cause of secondary hypertension in adults. It occurs particularly in patients with sexual maturation disorders such as precocious puberty, delayed puberty, or sexual infantilism.

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## Authorship Contributions

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