Case Report

# Treatment of Hypertension in a Child With 11Beta-Hydroxylase Deficiency: A Case Report

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## ABSTRACT

**Background:** 11beta-hydroxylase deficiency (11βOHD) is clinically presented with external genitalia virilization in girls and precocious puberty in boys. Low renin hypertension occurs in both sexes. Early diagnosis and treatment of hypertension can prevent complications.

**Objectives:** To provide a practical management for controlling hypertension in patients with 11-beta-hydroxylase deficiency.

**Methods:** We described a 4.5 years old girl of 46.XX, who presented with ambiguous genitalia at birth and hypertension later in follow-up. The patient had received the appropriate dosage of hydrocortisone and the level of 17-hydroxy progesterone was within the acceptable range but the hypokalemia persisted. Both hypertension and hypokalemia were normalized when spironolactone was added.

**Results:** Blocking mineralocorticoid receptor treat hypertension in 11-beta-hydroxylase deficiency.

**Conclusions:** Intermittent measurement of blood pressure is necessary for patients with 11βOHD. In these patients, spironolactone is effective in treating mineralocorticoid-mediated hypertension and hypokalemia by blocking mineralocorticoid receptors.

## 1. Introduction

11-hydroxylase deficiency (11βOHD) is an autosomal recessive disorder in the gene encoding CYP11B1 on the 8q24.3 chromosome (1). This steroid-dependent adrenal enzyme disorder is the second most prevalent cause of Congenital Adrenal Hyperplasia (CAH) after 21-hydroxylase deficiency, which accounts for 5-8% of cases and causes low-renin hypertension (2, 3). Systolic and/or diastolic blood pressure are increased in these patients (4). The incidence of 11βOHD is one in one hundred thousand live births born to unrelated parents (5). 11β-hydroxylation is an enzymatic reaction required for

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the biosynthesis of cortisol in the Zona Fasciculata (ZF) in the adrenal cortex. Disruption at this stage increases the production of steroid 11-deoxycorticosterone (DOC). DOC is a moderate-acting mineralocorticoid that renders sodium and volume retention, and hypertension consequently. High production of adrenal androgens causes prenatal virilization in females, and postnatal virilization in both sexes (6).

Due to a clinical similarity, 11βOHD may not be distinguishable from the simple virilizing form of 21β-hydroxylase deficiency simple virilizing (SV) and measurement of ACTH-stimulated adrenal steroids by LC-MS/MS prevents the misdiagnosis. Serum cortisol stimulated with ACTH (rather than 11-doxycortisol) is measured in the classical (<70 nmol/L) and non-classical (>160 nmol/L) types, respectively (7). Bilateral adrenalectomy is performed in cases of resistant hypertension, uncontrolled hyperandrogenism/virilization, and/or bilateral Cushing's syndrome (8, 9).

## 2. Case Presentation

The patient was a four and half years old child with a 46, XX karyotype, when she was admitted with a urinary tract infection to the Qazvin Children's Hospital, Iran, in January 2021. The child weighed 3150 g at birth and was born from a consanguineous marriage. At birth, she had sexual ambiguity stage IV of Prader and at the age of 18 months, she underwent genitoplasty. On admission, she had not any sign of precocious puberty.

Laboratory examination revealed hypokalemia of 2.1 mmol/l, normal LH and FSH levels, and high levels of adrenocorticotropin (ACTH), testosterone, 17-OH-progesterone, and DHEA-S with low plasma renin. Basal cortisol level was 0.8 µg/dl and rose to 1.1 µg/dl, 60 minutes after the ACTH stimulation test.

As a result, the patient was diagnosed with congenital adrenal hyperplasia due to 11-OHD and treated with hydrocortisone. In follow-up, the patient was hospitalized for the second time due to a urinary tract infection with flank pain, dysuria, and pyuria symptoms in the urine analysis and positive urine culture when she was four and half years old. Urinary retention, daily urinary incontinence, and constipation were listed in the patient's medical history. On examination, the peripheral pulses were hyperactive and the blood pressure was 160/90 mmHg (both systolic and diastolic blood pressure over 99% percentile). The patient weighed 23 kg in the 95% percentile and her height was 125 cm, over the 97% percentile for the given age and sex, respectively. Bone age was estimated to be 11 years in left hand and wrist graphs based on the Greulich and Pyle atlas. At the time of hospitalization, while the patient received hydrocortisone 3 mg every eight hours and the level of 17-hydroxy progesterone was within acceptable limits, hypokalemia was detected in the patient's tests. The child had no history of hospitalization due to adrenal insufficiency. The patient's test results are presented in Table 1.

Ophthalmic examination was normal. Echocardiography reported moderate left ventricular hypertrophy with normal ejection fraction (80%) and a mean stroke volume of 50.5 mL/s. Echocardiography results reported mild left ventricular hypertrophy two months later and with normal indices at six months of treatment. Renal ultrasonography reported the left and right kidney sizes, 78 mm and 80 mm respectively, while the bladder's volume was determined to be 115 cc and the urine residue was 49 cc. The adrenal glands and the right ovary were normal in terms of size, whereas the left ovary was smaller than normal. Renal Doppler ultrasound denoted that the inter-lobar arterial resistance was normal, while the arterial resistance was reported as 0.55 on the left and 0.61 on the right. Urodynamic studies (UDS) determined the bladder's volume of 337 cc, and the compliance was observed to be 30 cc per cm of water. The residual urine was 100 cc. The patient was advised to have timed voiding, the constipation was treated with propylene glycol, and an alpha-blocker prescription was provided to improve bladder emptying. After several months of follow-up, the urinary tract infection did not recur.

The patient was given a course of treatment that included atenolol 50 mg every 12 hours, enalapril 2.5 mg every 12 hours, and amlodipine 5 mg every 12 hours. Despite these medications, the patient's blood pressure was detected above 90% of the percentile for the given age, sex, and height and hypokalemia persisted as well. With the addition of spironolactone 25 mg to the treatment regimen every 12 hours, the patient's blood pressure gradually decreased to 100/60 (both systolic and diastolic blood pressure between 50 to 90% percentile), and also the serum potassium reverted to normal. Other antihypertensive drugs were gradually discontinued.

A psychiatric consult was requested due to lack of concentration and incomprehensive speech and with the diagnosis of cognitive developmental delay; thus, the patient was treated with speech therapy and ergo therapy.

## 3. Discussion

Congenital adrenal hyperplasia is a chronic life-long disease. In childhood, the CAH treatment focuses on gender assignment, genital reconstruction, sexual and physical growth, and development. The CAH treatment focuses on fertility, prevention of metabolic syndrome, and osteoporosis in line with the patient's growths. Treatment of CAH patients requires the participation of a team with an endocrinologist, urologist, gynecologist, psychiatrist, and geneticist (10). Typical manifestations of this disease include low-renin hypertension, hypokalemia, hyperandrogenism, and sexual ambiguity in females (11). Approximately two-thirds of patients with 11βOHD suffer from hypertension that arises in the early years of life, as a result of deoxycorticosterone accumulation in the zona fasciculata and mineralocorticoid effects. Increased mineralocorticoids reduce potassium and cause sodium retention (7). Nonclassical 11OHD deficiency must be regarded as a major differential diagnosis in patients with unexplained hyperandrogenism without impaired sexual development (12).

Goyal et al. introduced a 46.XX child, who showed symptoms of premature puberty and hypokalemic hypertension at the age of three. Diagnosis of 11βOHD was made based on clinical and laboratory results. Hypertension and hypokalemia improved following the treatment course of glucocorticoids. Hysterectomy, oophorectomy, and breast resection operations were performed to maintain a male appearance at the age of 13 (1). In the study by Yildiz et al, the clinical and laboratory characteristics of 102 children from 76 families with biallelic CYP11B1 mutation were examined. Ten percent of 46, XX patients grew up as males. Nineteen percent of patients were initially misdiagnosed with a 21-hydroxylase deficiency. Due to the increase in androgen levels in these patients, especially in those who do not have good control, bone age progresses, and as a result, the final height of these patients is shortened and the average height of adult men and women is about 152 cm and 160.4 cm, respectively. The average height of adult men and women was 152 cm and 160.4 cm, respectively. Also, 11-oxygenated androgens and 21-deoxycortisol levels were low in all patients (13). Our patient's bone age was also much more advanced than her chronologi-

**Table 1.** Laboratory tests of the patient

| Laboratory Data | Median (IQR) |
|---|---|
| 17OH-progestrone (nmol/L) | 3.2 (3-10) |
| Aldosterone (nmol/L) | 0.22 (0.08-3.60) |
| WBC (/µl) | 4700 (4500-10000) |
| RBC (/µl) | 4.8 (4.7-6.1) |
| Platelet (/µl) | 168000 (150000-450000) |
| PH | 7.43 (7.35-7.45) |
| PCO2 (mmHg) | 29 (35-45) |
| HCO3- (mEq/L) | 20 (20-24) |
| BUN (mg/dl) | 11 (5-18) |
| Cr (mg/dl) | 0.7(0.3-0.9) |
| Na (mEq/L) | 136 (135-145) |
| K (mEq/L) | 2.6 (3.5-5.5) |
| Cl (mEq/L) | 105 (95-105) |
| T4 (mcg/dl) | 9 (5.95-14.7) |
| TSH (U/L) | 1.2 (0.32-6.2) |

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IQR: Interquartile range; To convert nmol/L to ng/mL, divide by 2.77 for aldosterone; 3.03 for 11-deoxycorticosterone. BUN: Blood Urea Nitrogen; Cr: Creatinine; T4: Thyroxin; TSH: Thyroid Stimulation Hormone.

cal age, which is due to irregular administration of hydrocortisone by the mother in the first three years of life.

Hamza et al. introduced cases of 11βOHD patients: two with obesity and hypertension, and three with stunted growth and hypokalemia. The first case was a 37-year-old male with a 46, XY karyotype, born to consanguineous parents and diagnosed at the age of three with symptoms of premature puberty, pubic hair growth, and increasing bone age. At the age of 25, the patient suffered from grade 3 hypertension with hypokalemia, both of which were treated with amlodipine, atenolol, and hydrocortisone. Adrenal insufficiency did not occur during follow-up despite the low compliance to the treatment. The patient suffered from abdominal pain attacks, which improved following the treatment of hypokalemia. Spironolactone was added to his medical regimen at the age of 36 due to persistent hypokalemia. The second case was a 35-year-old female diagnosed with 11βOHD in infancy and later underwent surgery for genital virilization repair. The patient had high blood pressure and hypokalemia, and she was first treated with hydrocortisone. She developed adrenal insufficiency in the course of treatment. The third case was a 28-year-old female with metabolic syndrome, obesity, and polycystic ovary syndrome. The serum testosterone was measured at 6.2 ng/ml, and she was further diagnosed with hyperandrogenism. With increasing the hydrocortisone dose, the patient lost weight and menstrual cycles were returned (5). Our patient's blood pressure was not initially controlled with enalapril, atenolol, and amlodipine but returned to normal with spironolactone.

Valsalan introduced a 19-year-old patient with 46.XX karyotype, ambiguous genitalia, and hypertension, born to consanguineous parents. Clinical symptoms included premature fatigue, shortness of breath on exertion, blurred vision, and chest pain. Short stature, gynecomastia, hyperpigmentation, and a low-pitched voice were observed upon examination. Her blood pressure was 170.120, with cardiomegaly and hypertensive retinopathy. Tests denoted hypokalemia as well (14). In Wang's report, a 23-year-old girl (46. XX) with a hypertension diagnosis at the age of 14 with a BMI of 20.8 kg/m$^2$ was reported. Nifedipine treatment maintained partial blood pressure control. The patient had relative masculinization and the labia development had not been abnormal. Following the non-classical 11OHD diagnosis, the patient was given hydrocortisone and spironolactone treatment. The patient's blood pressure was well-controlled and the masculinization symptoms reverted to normal with a decrease in androgen levels (11).

In Dittmann's report, the cognitive-developmental delay was observed in patients with 11βOHD. In earlier studies, females with congenital adrenal insufficiency had displayed an IQ equal to that of their sisters. Differences in IQ, information, and similarities were observed in salt-wasting and simple-virilizing girls with their sisters (15). In Hamed et al.'s study, most females with CAH displayed introverted and extroverted behavioral disorders, while emotional, conduct, hyperactivity, and attention deficit symptoms were more pronounced than their peers. Bone age and 17-IHP, testosterone, and androstenedione levels were independently associated with behavioral issues. Behavioral issues in these females were due to inadequate steroids and androgens (16).

## 4. Conclusion

11β-hydroxylase deficiency is a rare type of CAH with autosomal recessive inheritance. Inborn errors of steroid biosynthesis in these patients cause clinical manifestations of sexual ambiguity in 46 XX girls, mineralocorticoid excess, pseudo-precocious puberty, and accelerated growth rate with short final height. Important points in the treatment of these patients are glucocorticoid replacement, and control of hypertension to prevent end-organ damage. In our patient, in addition to glucocorticoid administration, the patient's blood pressure and hypokalemia were controlled with low-dose spironolactone monotherapy.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles are considered in this article. The participant and their parents were informed of the purpose of the research. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the parents. Principles of the Helsinki Convention was also observed. This study was approved by the Ethics Committee of the Medical University of Qazvin (Code: IR.QUMS.REC.1400.123).

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### Authors' contributions

All authors equally contributed to preparing this article.

## Conflicts of interest

The authors declared no conflict of interest.

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