A Rare Case of Hypertension in a Young (Fe)male

Sir,

Congenital adrenal hyperplasia (CAH) is a syndromic disease resulting from defects in various enzymes in the pathway of steroidogenesis. The most common form of CAH is 21 alpha hydroxylase deficiency. 17 alpha Hydroxylase deficiency is a rare form of CAH, with an estimated incidence of 1 in 50,000–100,000 individuals, and represents ~1% of all CAH cases.[1,2] The first case of 17 alpha hydroxylase deficiency was reported in 1966 by Biglieri *et al*.[3]

We report a case of a 32-year-old female patient who presented with the chief complaints of weakness of all the four limbs for the last 5 days, which were not associated with sensory and cranial disturbances. She was a nondiabetic and a known hypertensive since 2 years; she had no significant past history except for not attaining menarche and was diagnosed with atrophic uterus by a gynecologist during her childhood.

On examination, the patient was moderately built and well-nourished with a height of 178 cm, weight of 74 kg (BMI: 23.4 kg/m^2), and an arm span of 172 cm. She had poorly developed secondary sexual characters with a lack of normal breast development (B1) and

absent axillary and sparse pubic hair (Stage III). Bilateral palpable inguinal swellings were noticed. Her BP was 140/90 mmHg on presentation. Investigations showed serum creatinine of 2.6 mg/dl, LH of 74 mIU/ml (normal range 0.5–16.9 mIU/mL), Follicle-stimulating hormone (FSH) of 91.50 mIU/ml (1.5–9.1 mIU/ml), progesterone of 12.95 ng/ml (normal level: follicular phase: 0.3–0.8 ng/ml, luteal phase: 4–20 ng/ml), adrenocorticotropic hormone (ACTH) of 77.8 pg/ml (0–46 pg/ml), and prolactin of 29.4 ng/ml (4.7–23.3 ng/ml) were elevated. However, her aldosterone of 9.2 ng/dl (7–340 ng/ml), cortisol of 1.50 μg/dl (5–25 μg/dl), testosterone of 0.03 ng/ml (0.08–0.6 ng/ml), and potassium levels of 2.5 mmol/l were decreased [Table 1]. Twenty-four-hours urinary potassium was 10 meq/day. Low urine K level could be due to the very low serum potassium at the time of testing. Arterial blood gas (ABG) analysis showed metabolic alkalosis (pH: 7.42;: 30 mmol/l; $PaCO_2$ 42 mmHg). Ultrasonography of the abdomen and the pelvis showed absent uterus and ovaries. There was evidence of two well-defined hypoechoic structures with internal vascularity noted in bilateral inguinal regions likely to be testis, and also bilateral grade I/II renal parenchymal changes were noted. Renal biopsy was suggestive of hypertensive nephrosclerosis. Bilateral fundus examination revealed Grade I hypertensive retinopathy changes. 2D echo and renal artery Doppler were normal. Cytogenetic analysis was done by Giemsa (GTG) banding and the result was of a male karyotype (46XY). The patient's clinical, hormonal, and metabolic characteristics were typical of 17 alpha hydroxylase deficiency. The patient was started on prednisolone (10 mg/day) and ethinyl estradiol 10 μg/day. Lifestyle modifications were advised and anti-hypertensives were continued. After 4 weeks, antihypertensives were tapered and stopped completely. Her blood pressure and potassium levels were normal at 6 weeks after discharge. She was continued on hormonal therapy and urologist opinion was taken regarding orchidectomy of both testes, as there is a chance of malignant transformation for which surgery was planned at a later date.

Table 1: The plasma steroids, androgens, and pituitary hormonal levels along with the reference ranges

Investigation	Result	Reference range
Creatinine	2.6 mg/dl	0.7-1.2
Sodium	146 mmol/l	135-145
Potassium	2.50 mmol/l	3.5-5
Cortisol	1.50 μg/dl	M: 6.2-19.4; E: 11.9
Testosterone	0.03 ng/ml	0.2-1
FSH	91.50 mIU/ml	1.5-12
LH	74.60 mIU/ml	1.7-8.6
Prolactin	29.40 ng/ml	3.4-24
Aldosterone	9.2 ng/dl	At rest: 1-16, in motion: 3.5-30
Plasma renin	0.04 ng/ml/h	
11DOC	124 pg/dl	3.76-4.20

CAH is a spectrum that results from defects in various enzymes in the pathway of steroidogenesis. Pregnenolone, which is the common precursor for the steroid synthesis, is produced from the cholesterol. It is further metabolized by various enzymes to produce glucocorticoids, mineralocorticoids, adrenal androgens, and sex hormones. 17 alpha Hydroxylase helps in the metabolism of pregnenolone and progesterone through a chain of reactions to finally produce sex steroids and glucocorticoids. Its deficiency results in decreased production of the cortisol and the adrenal androgens and sex steroids. Genetic females (46XX) with complete deficiency of 17 alpha hydroxylase have primary amenorrhea and no pubertal development leading to hypoplastic breasts and lack of axillary and pubic hair. Genetically, male (46XY) patients have an absence of masculinization. However, normal Mullerian duct regression occurs because of normal production of Mullerian inhibitory factor from the testis. Thus, such patients have a blind vagina, absence of Mullerian structures (fallopian tubes and uterus, upper third of the vagina), and female external genitalia. Pregnenolone and progesterone increase the mineralocorticoid pathway resulting in an increase in 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone levels.[4,5] In healthy individuals, decreased cortisol synthesis and the subsequent loss of feedback inhibition on pituitary ACTH lead to an increase in ACTH release, in order to return cortisol production to normal levels. However, in CAH patients, overstimulation of the steroid synthetic pathway leads to the overproduction of mineralocorticoid precursors and hyperplasia of the adrenal cortex. High levels of mineralocorticoid precursors (11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) induce sodium and fluid retention, and loss of potassium and hydrogen, which consequently induces hypertension and hypokalemic alkalosis and flaccid paralysis.[6] Hypertension was attributed to be the cause of renal failure in this patient,[7] as biopsy showed that hypertensive changes and both eyes had grade 1 hypertensive retinopathy Recognition of 17OHD is difficult even after puberty; therefore, inappropriate managements are frequently encountered. Neonatal screening for CAH due to 21-α-hydroxylase deficiency can be done by measuring 17 alpha hydroxyprogesterone levels between 2 and 4 days after birth.[8] However, the screening programs of 17-α-hydroxylase deficiency, which is relatively rare, have not been well described in the literature, but probably the levels of corticosterone, deoxycorticosterone, 18-hydroxy Deoxycorticosterone, Deoxycorticosterone and 18 hydroxycorticosterone can be tested as these are bound to increase in 17 alpha hydroxylase deficiency.

The mainstay of treatment is glucocorticoid therapy. Spironolactone is usually used as an antihypertensive agent and for the control of hirsutism in CAH; however, as our patient is a female phenotype (XY) with 17-α-hydroxylase

deficiency, it can be used as an antihypertensive rather than for the control of hirsutism.

Due to the low incidence of adrenal crisis and other severe symptoms in untreated 17OHD, the diagnosis is often delayed. Patients usually present around adolescence or at the pubertal age and the awareness of the clinician about this condition is very important so that diagnosis should not be missed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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