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17-Alpha Hydroxylase Deficiency: A Rare Case of Primary Amenorrhea and Hypertension

17-Alfa Hidroksilaz Eksikliği: Primer Amenore ve Hipertansiyonla Seyreden Nadir Bir Olgu

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Abstract

17-alpha hydroxylase deficiency (17OHD) is an uncommon cause of congenital adrenal hyperplasia (CAH) resulting from mutation in the CYP17 gene. It is an autosomal recessive disease leading to the deficiency of enzyme activity which results in impaired synthesis of cortisol, androgen and sex steroids. A 35-year-old woman was admitted to the hospital with hypokalemia, weakness, and fatigue. Medical history revealed two attempts of in vitro fertilization (IVF) without achieving pregnancy. Laboratory evaluation showed hypokalemia, hypocortisolemia, hypergonadotropic hypogonadism and increased levels of 11-deoxycorticosterone. Her karyotype was 46XX. The patient had no history of menarche. She had Tanner stage 2 breast development. Genotyping showed homozygous mutation located in exon 7 which abolishes both 17-alpha hydroxylase and 17,20 lyase activities of the CYP17A1 protein. After starting dexamethasone 0.5 mg/day, her potassium level was normalized, and blood pressure improved. In conclusion, a comprehensive evaluation should be performed before using assisted reproductive techniques, such as in vitro fertilization in hypertensive women with sexual infantilism, primary amenorrhea, and hypokalemia. *Turk Jem 2014; 18: 137-139*
Key words: 17-alpha hydroxylase deficiency, primary amenorrhea, in vitro fertilization, congenital adrenal hyperplasia

Özet

17-alfa hidroksilaz eksikliği, CYP17 geninde meydana gelen mutasyon sonucu oluşan konjenital adrenal hiperplazilerin nadir bir formudur. Otozomal resesif geçişlidir. Enzim aktivitesindeki defekt kortizol, androjen ve seks steroidlerinin sentezinde bozulma ile sonuçlanır. Otuz beş yaşında kadın hasta hastaneye halsizlik ve yorgunluk şikayetleriyle başvurdu. Hikayesinde spontan menarş, pubarş olmadığı ve iki defa başarısızlıkla sonuçlanan in vitro fertilizasyon (İVF) denemesi olduğu öğrenildi. Meme gelişimi tanner II ile uyumluydu. Laboratuvar değerlerinde hipokalemi, hipokortizolemi, hipergonadotropik hipogonadizm ve artmış 11-Deoksikortikosteron ile uyumlu bulguları vardı ve karyotipi 46XX'ti. Genetik incelenmesinde ekzon 7'de lokalize homozigot mutasyon saptandı. Hastaya deksametazon 0,5 mg/gün başlandıktan sonra potasyum seviyeleri normale gelirken kan basıncı regüle oldu. Sonuç olarak, İVF gibi üreme teknikleri uygulanmadan önce hipertansiyonla birlikte primer amenoresi, hipokalemisi ve cinsel gelişimi yetersiz olan kadınların kapsamlı bir şekilde değerlendirilmesi gerekmektedir. *Turk Jem 2014; 18: 137-139*
Anahtar kelimeler: 17-alfa hidroksilaz eksikliği, primer amenore, in vitro fertilizasyon, konjenital adrenal hiperplazi

Introduction

17-alpha hydroxylase (17OHD) deficiency is an uncommon cause of congenital adrenal hyperplasia (CAH) resulting from mutation in the CYP17 gene (1). The gene is expressed in the adrenal gland and gonads. 17OHD catalyzes two successive reactions: 17α hydroxylation of pregnenolone and progesterone, and 17,20-lyase reaction of the 17α-hydroxylated products (2). 17OHD is an autosomal recessive disease leading to the deficiency of enzyme activity which results in impaired synthesis of cortisol, androgen and sex steroids. Additionally, it results in an elevation of ACTH secretion and consequent overproduction of mineralocorticoids. The disease is characterized by hypertension, hypokalemic alkalosis and deficient secondary sexual characteristics; with primary amenorrhea in females and 46 XY disorder of sex development (DSD) in males as distinctive clinical features (3). Features of DSD in males may be small phallus, cryptorchidism, pseudovaginal pouch, and perineal hypospadias. It was first described in 1966 (4), and to date, nearly 150 cases of 17OHD have been reported (5). Herein, we present a female patient with both clinical and hormonal characteristics of 17OHD who has been treated inadequately before the current diagnosis. Our aim is sharing our experiences about this very rare disease.

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Case Report

A 35-year-old woman was referred to Erciyes University Medical School, Department of Endocrinology because of persisting hypokalemia, weakness, and fatigue. She reported neither spontaneous menarche nor pubarche in her medical history. Her puberty was induced by using oral contraceptive agents. She had used oral contraceptive agents regularly until her demand of pregnancy. She was admitted to an infertility clinic in another hospital when she was 25 years old. Her medical history showed that in vitro fertilization (IVF) was tried twice but no pregnancy was achieved. At that time, she had hypertension with hypokalemia. However, no further examination was performed for the etiology of hypokalemia and hypertension in this young woman. Briefly, she had primary amenorrhea, mild polyuria, hypokalemia, infertility, and hypertension. Physical examination revealed blood pressure of 150/100 mmHg, body mass index of 24 kg/m^2, breast development tanner II, and atrophic cervix.

On laboratory evaluation, she had hypokalemia, diabetes mellitus, primary adrenal insufficiency, hypergonadotropic hypogonadism, and increased levels of 11-deoxycorticosterone, progesterone, and sodium (Table 1). Serum progesterone being the immediate proximal hormone, prior to 17-hydroxy progesterone was elevated confirming the diagnosis of 17OHD. The computed tomography of the adrenal glands revealed bilateral adrenal thickening (Figure 1). Her karyotype was 46XX. The clinical and laboratory findings in addition to adrenal enlargement raised the possibility of 17OHD. Hormonal investigations were compatible with 17OHD and genotyping showed homozygous p.P409L (c.1226 C>T) mutation located in exon 7 which abolishes both 17OHD and 17,20 lyase activities of CYP17A1 protein (6).

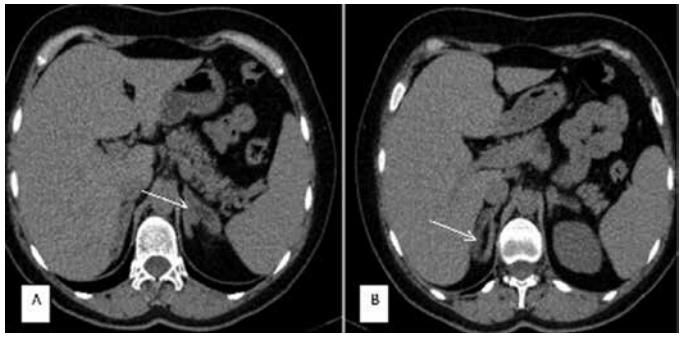

Figure 1. Images of the bilateral adrenal thickening on CT. A: Left adrenal gland, widest thickening 27 mm. B: Right adrenal gland, widest thickening 14 mm

After starting dexamethasone 0.5 mg/day, her potassium level normalized, and blood pressure became normal. In addition, metformin (2000 mg/day) was given for the treatment of diabetes mellitus.

Discussion

17OHD is a rare autosomal recessive form of CAH. It accounts for approximately 1% of all cases with CAH (7). It results in decreased androgens, cortisol, estrogen whilst increased ACTH, FSH, LH levels (3,8). The cortisol levels in patients without treatment are low, but they do not have severe symptoms of cortisol deficiency, because corticosterone has glucocorticoid activity. Thus, our patient did not present with symptoms of cortisol deficiency. Patients with 17OHD usually present with hypertension, hypokalemia and delayed puberty and, our patient had all of them. She had severe hypokalemia, hypertension and infertility. 17OHD activity is normally present in either adrenals or gonads (9), and therefore, most patients are hypertensive and hypogonadal (10).

Both primary renal disorders and endocrine disorders (apparent mineralocorticoid excess syndrome and other uncommon forms of congenital adrenal hyperplasia) may cause hypokalemia, hypertension and infertility (11). Therefore, differential diagnosis for such a patient has to be made carefully by laboratory and imaging studies.

Glucocorticoid therapy is essential for the amelioration of hypertension, hypokalemia and mild adrenal insufficiency (8). However, in women, fertility is generally difficult, because egg maturation and ovulation are not sufficiently supported by the steroid production of ovaries.

Due to the low incidence of adrenal crisis and other severe symptoms in untreated 17OHD, the diagnosis often delays. Recognition of 17OHD is difficult even after puberty, therefore, inappropriate managements are frequently encountered. For instance, IVF in the presented case is not a logical treatment option for pregnancy. Deficiency of 17-OH enzyme is caused by mutation of the CYP17 gene. More than 50 mutations have been reported so far (12,13). Recent studies showed that cytosine to

Table 1. Laboratory findings of the case

	Patient's value	Reference value		Patient's value	Reference value
Glucose	141	74-100 mg/dL	ACTH	863	0-46 pg/mL
BUN	12	8-26 mg/dL	Cortisol	3.9	5-25 µg/dL
Creatinine	0,8	0.7-1.3 mg/dL	11-Deoxy cortisol	1.6	0-8 ng/mL
Na	147	136-145 mmol/L	FSH	17.7	1.5-9.1 mIU/mL
K	2.4	3.5-5.5 mmol/L	LH	29.1	0.5-16.9 mIU/mL
Cl	111	99-109 mmol/L	Estradiol	15	<11.8 pg/mL (lowest value)
Prolactin	16	4.7-23.3 ng/mL	Progesterone	46	1.7-27 ng/mL
Aldosterone	404	35-300 pg/mL	17-OHP	2.8	0-2 ng/mL
Plasma renin activity	0.13	1.9-6.0 ng-mL/h	11-DOC	3.74	0.1-0.6 pmol/mL

guanin transition in exon 7 can cause a substitution of the amino acids, proline and arginine (12). We also found a mutation in exon 7 in our case which may let us think that amino acid 409 is prone to be mutated.

In conclusion, this case report emphasizes that CAH due to 17OHD should be considered in adult hypertensive female patients with sexual infantilism, primary amenorrhea, hypokalemia as well as male patients with ambiguous or feminine external genitalia. Importantly, before using expensive assisted reproduction techniques, such as IVF in an amenorrheic woman, a clinical, hormonal and eventually molecular evaluation should be performed to establish the correct diagnosis.

Conflicts of Interest

There are no conflicts of interest.

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