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A Rare Cause of Delayed Puberty in Two Siblings: A Case Report

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Abstract

Introduction: 17 alpha-hydroxylase deficiency (17-OHD) is an infrequent autosomal recessive disorder in adrenal and gonadal steroidogenesis due to the *CYP17A1* defect. Affected girls are characterized by delayed puberty, absence of secondary sex characteristics at puberty, and primary amenorrhea. Affected boys show female or ambiguous genitalia. Hormone imbalances result in varying degrees of hypertension and hypokalemia. The increase in corticosterone levels prevents the development of typical adrenal insufficiency symptoms. Glucocorticoid and sex steroid supplementation is the preferred treatment.

Case Presentation: We reported two phenotypically female siblings, aged 14 and 25 years, with the 17-OHD from Ankara, the capital city of Turkey. The younger child had a 46,XX karyotype and the older had a 46,XY chromosome pattern. Another feature of the second patient (aged 25 years), was the presence of a large myelolipoma in her right adrenal gland.

Conclusions: 17 alpha-hydroxylase patients are usually diagnosed late, and unlike patients with other forms of congenital adrenal hyperplasia, hypertension is the major finding, and 10% - 15% of patients have normal blood pressure at diagnosis. The delay in diagnosis causes hypertension and renovascular changes, psychological problems, osteoporosis, and irreversible damage to breast tissue.

Keywords: 17 Alpha-Hydroxylase Deficiency, Puberty, Delayed Diagnosis

1. Introduction

17 alpha-hydroxylase deficiency (17-OHD) is a very infrequent type of congenital adrenal hyperplasia (CAH). Loss-of-function mutations in *CYP17A1* can result in 17-OHD. This gene is located on chromosome 10q24-3 and contains eight exons with a length of 1870 bp, translating into a 508 amino acid polypeptide containing a cytochrome p450 domain encoded between codons 28 to 493. Currently, over 100 mutations in the *CYP17A1* gene have been identified (including point mutations, small deletions/insertions, duplications, frameshift mutations, and rarely, large deletions). The resulted disease is autosomal recessive inheritance (1); accordingly, parental consanguinity is an important risk factor. The gene is expressed in both adrenals and the gonads. Although prevalence data are lacking, it is estimated to be seen in approximately < 1 per 100,000 live births (1). The most common presentation of 46,XY patients is ambiguous or female genitalia with inguinal hernia. Hypertension and hypokalemia are also possible. The most severely affected cases are born with characteristically female external genitalia and are generally raised as females. Therefore, patients with apparent female genitalia may remain undiagnosed until puberty (1, 2). Although the external genitalia is normal in 46,XX patients, the most common presentation is an adolescent girl with primary amenorrhea, delayed secondary sexual characteristics, and manifesting varying degrees of hypertension and hypokalemia.

As cortisol synthesis is blocked, adrenocorticotropic hormone (ACTH) levels increase and stimulate the production of 11-deoxycorticosterone (DOC) and corticosterone, which have strong mineralocorticoid activity.

Adrenal crisis typically does not develop in these patients due to increased corticosterone (3). DOC excess leads to suppression of the renin-angiotensin-aldosterone system, reduces aldosterone production, and results in hypertension and hypokalemia, whereas 10% - 15% of 17-OHD patients are normotensive at diagnosis. The absence of 17,20-lyase activity in the adrenal gland also results in the deficiency of dehydroepiandrosterone sulfate (DHEAS), causing failure of adrenarche and pubic and axillary hair development. We reported a case of two 46,XY and 46,XX siblings with 17-OHD.

2. Case Presentation

A 14-year-old girl from Ankara, Turkey referred to the pediatric endocrinology outpatient with the lack of sec-

ondary sexual characteristics and primary amenorrhea in 2018. The patient had not relevant medical history, such as chronic illness, drug use, weight loss, or stress. Her parents were first cousins. On physical examination, height was 157 cm and body weight was 56 kg (0.37 SDS). Blood pressure was 120/90 mm/Hg and her external genitalia showed vaginal openness. The general physical and sexual development was compatible with Tanner stage 1. Laboratory test results showed normal levels for blood cell counts and renal and liver function tests results were within normal range. Serum sodium was 139 mEq/L (135 - 145) and potassium was 3.98 meq/L (3.5 - 5.5). Hormone levels were as follows: plasma follicle stimulating hormone (FSH): 104 mIU/mL, luteinizing hormone (LH): 27 mIU/mL, testosterone: 0.14 ng/dL (0.1 - 0.75), estradiol: < 20 pg/mL, ACTH: 154 pg/mL (0 - 46), cortisol: 0.49 μg/dL (6.7 - 22), DHEA-S: < 15 mcg/dL (35 - 430), plasma renin activity: 0.55 ng/mL/h (3.18 - 32.61), aldosterone: 5 ng/dL (2 - 22), 17-OHP: < 0.04 ng/dL (0.2 - 2), dehydrotestosterone: 2.4ng/dL (40 - 170), 11-deoxycortisol: < 0.02 ng/dL (0 - 344), and progesterone: 9.77 ng/mL (N: 0.03 - 0.9) (Table 1).

Table 1. Laboratory Test Results of the Patients

	Patient 1	Patient 2
Age (years)	14	25
Na/K (mEq/L)	139/3.98	140/3.29
Acth (pg/mL)	154	101
Kortisol (μg/dL)	0.49	0.49
Lh (mıu/mL)	27	28
Fsh (mıu/mL)	104	92
Estradiol (pg/mL)	< 20	< 20
Testesteron (ng/dL)	0.14	< 0.1
DHEA-S (μg/dL)	< 15	< 15
PRA (ng/mL/h)	0.55	0.88
Aldosteron (ng/dL)	5	4
17-OH progesteron (ng/mL)	< 0.04	< 0.04
Progesteron (ng/mL)	9.77	8.7
11.doc (ng/dL)	< 0.02	< 0.02
Karyotype	46 XX	46 XY
Mutation	Large deletion of exons 1 - 6	Large deletion of exons 1 - 6

Pelvic ultrasound showed an infantile uterus measuring 28 x 20 x 4 mm. The endometrium was not clearly visible, and the corpus-to-cervix ratio was < 1. In the left adnexal area, a mass resembling a gonad was observed, 22 x 14 x 6 mm (0.9 cm^3) in size, and another gonad-like mass 18 x 12 x 12 mm (1.3 cm^3) in size was observed in the right adnexal area. Suspected cysts were also seen.

A high-dose ACTH stimulation test (synacthen test) showed a peak cortisol response of 0.56 μg/dL. There was no hypertension on 24-hour blood pressure monitoring. Serum potassium levels were near low limits (between 3.7 - 3.9 mEq/L). The karyotype was determined as 46,XX. Genetic analysis revealed a large deletion (exons 1 - 6) in the *CYP17A1* gene. Consequently, estrogen replacement therapy was initiated to induce the development of secondary sex characteristics and oral hydrocortisone (10 mg/m^2 per day) for the prevention of hypertension. The bone mineral densitometer z score was -2.1; therefore, vitamin D and calcium treatments were started. After approximately 2 years of sex steroid replacement therapy, breast development progressed to Tanner stage 4 and pubic hair was at stage 2.

The patient's family history revealed that her older sibling, now 25 years old, also had the same symptoms. On physical examination, she was tall and thin (178 cm in height and 60 kg in weight) with a blood pressure of 160/100 mmHg. There was no breast development or any pubic and axillary hair. At the age of 14, she had undergone surgery for bilateral inguinal masses, with no further information on this procedure available. However, the patient had refused additional medical treatment. Laboratory investigations revealed a normal blood count and the results of renal and liver function tests were within the normal range. Serum sodium was 140 mEq/L and potassium was 3.29 meq/L. Hormonal evaluation showed the following results FSH: 92 mIU/mL, LH: 28 mIU/mL, testosterone: < 0.1 ng/dL (0.1 - 0.75), DHEAS: < 15 mcg/dL (35 - 430), cortisol: 0.49 μg/dL (6.7 - 22), plasma renin activity: 0.88 ng/mL/h (3.18 - 32.61), aldosterone: 4 ng/dL (3 - 16), ACTH: 101 pg/mL (0 - 46), 17-OHP: < 0.04 ng/dL (0.2 - 2), dihydrotestosterone: 2.4 ng/dL (40 - 170), 11-deoxycortisol: < 0.02 ng/dL - 344), and progesterone: 8. 7 ng/mL (0.03 - 0.9) (Tables 1 and 2). Karyotype analysis revealed a 46,XY karyotype. Genetic analysis showed a large deletion in exons 1 - 6 of the *CYP17A1* gene, the same mutation as her sibling. On magnetic resonance imaging, neither ovaries nor uterus could be detected, but 20 x 7 mm right adrenal myelolipoma was observed. Estrogen replacement therapy and hydrocortisone were initiated. The bone mineral densitometer result was -4,2; thus, vitamin D and calcium treatments were started. The patient was evaluated for the peripheral effects of hypertension. The echocardiographic and eye examination were normal for hypertension. The blood pressure became normal after starting treatment and there was no requirement for hypertensive drugs. Breast development stayed steady at Tanner stage1 during 1 year of treatment. The patient developed depressive symptoms and mood disorder; thus, antidepressant medication was started after a psychiatric consultation.

Table 2 . Patients Clinical Characteristics

Characteristics	Patient 1	Patient 2
Age (years)	14	25
Complaint	Primary amenorrhea, absence of secondary sexual characteristics	Primary amenorrhea, absence of secondary sexual characteristics
Weight (kg)	56	60
Height (m)	1.57	1.78
Blood pressure (mmHg)	120/90	160/100
Pubertal stage	Tanner stage 1	Tanner stage 1
Bone mineral density z score	-2.1	-4.2
Phenotype	Female	Female
Imaging study	Infantile uterus, small ovaries	Neither ovaries nor uterus could be detected. 20 x 7 mm right adrenal myelolipoma.
After pubertal treatment stage	Tanner stage 4, pubic hair stage 2	Tanner stage 1, pubic hair stage 1

2.1. Biochemical Analyses

Biochemical assessments were made in the biochemistry and endocrinology laboratories of the Bilkent city hospital (in a quality certified clinical laboratory). ACTH and renin were measured by chemiluminescence immunoassay and cortisol, estrogen, FSH, LH, progesterone, and testosterone levels were detected by electrochemiluminescence immunoassay. Also, DOC was measured by radioimmunoassay and the rest of the hormones were analyzed by enzyme-linked immunosorbent assay (ELISA). Calibration of the equipment was done every 3 months in Bilkent City Hospital.

3. Discussion

Due to 17-OH deficiency; Blockage of the relevant pathway caused overproduction of aldosterone, 11-DOC, corticosterone, whereas a decrease in cortisol, 17α-hydroxypregnenolone, 11-deoxycortisol, DHEA, testosterone, and androstenedione (4). The mineralocorticoid activity of DOC leads to sodium and fluid retention and loss of potassium, resulting in hypertension. Due to the increased production of corticosterone, adrenal insufficiency is not as obvious as classical Addison's disease. Although approximately 90% of the patients are hypertensive or hypokalemic on presentation, 10% - 15% have normal blood pressure at diagnosis, and because hypokalemia and hypertension cannot be seen in these cases, diagnosis can be difficult in this group (5). Our case was a patient with 46,XX karyotype with a normal potassium level and no hypertension, and her sibling had a 46,XY karyotype, hypokalemia, and hypertension.

The diagnosis of 17-OHD is based on biochemical, clinical, and genetic features. It depends on the type of mutations in the *CYP17A1* gene when different clinical and biochemical findings are encountered. Therefore, genetic analysis is very important to verify the diagnosis (1). However, the correlation between the *CYP17A1* genotype and phenotype remains unclear. Different clinical signs may be seen in patients with the same mutations, and even the severity of hypokalemia and hypertension and the initial variability may differ even among patients. A case reported by Athanasoulia et al. (5) had mild diastolic hypertension and normokalaemia, whereas four siblings reported by Deeb et al. (6) and a case reported by Brooke et al. (7) had notable hypertension and hypokalemia.

There was a large deletion in exons 1 - 6 of the *CYP17A1* gene in both cases. One patient had no hypertension and no hypokalemia, whereas the other was both hypertensive and hypokalemic. This clinical heterogeneity can be explained by the degree of enzyme deficiency, genetic susceptibility of hypertension, and environmental factors (1). The time of hypertension onset, the degree of hypokalemia, and aldosterone production appear to vary, even among cases with mutations that fully inactivate the enzyme (1, 4).

Reduced sex steroids can lead to the loss of feedback to the pituitary gland, resulting in increased levels of FSH and LH, in addition to oversized and cystic ovaries (5). However, in the current case, despite the high level of gonadotrophin, the ovaries were reported to be non-cystic and smaller than normal in size.

Treatment of 17-OHD includes glucocorticoid and sex steroid hormone supplementation. Glucocorticoid therapy prevents the adrenal insufficiency that may occur in stress situations and normalized blood levels of 11-DOC and ACTH (in this way blood pressure and serum electrolyte become normal levels). In 46, XX patients, estrogen replacement therapy can be administered to produce secondary sex characteristics, develop uterus, and prevent osteoporosis (1, 5). In 46, XY patients without signs of virilization, bilateral orchidectomy, and estrogen replacement therapy are treatment choices.

Breast development is poor in patients with late diagnosis. Athanosoulia et al. (5) reported a 17-year-old 46,XY patient who had presented with amenorrhea and mild diastolic hypertension. It has assumed that high progesterone levels during pubertal development can have an irreversible impact on breast tissue. In our first case, the breast responded very well to estrogen therapy, whereas in the second case, there was an insufficient response. In the first case, pubic hair progressed to Tanner stage 2 after

treatment. The application of dermal pomade containing estrogen has been shown to cause the growth of pubic hair in both males and females (8). It can be speculated that estrogens may also have a stimulatory influence on hair follicles, either directly or by increasing local androgen production.

Another feature of our second patient (aged 25 years) was the presence of a large myelolipoma in her right adrenal gland. Myelolipoma is an infrequent benign neoplasm of the adrenal gland and occurs in mature adipose and hematopoietic tissues (9). It is the second most common primary adrenal incidentaloma following adrenocortical adenomas. To date, fewer than 50 cases have been reported as symptomatic on presentation (9). The association between myelolipoma and CAH is rare. Adrenal myelolipoma is generally observed in patients with adrenal 21-hydroxylase deficiency. Although the etiology of myelolipoma in CAH is not clear, there are different theories attempting to explain the pathogenesis of myelolipomas; for example, the chronic ACTH stimulation causes metaplasia of adrenocortical cells, leading to myelolipoma (9). Most of these patients have remained untreated and exposed to elevated ACTH for long periods. Therefore, examination and screening of the adrenal glands in patients with 17-OHD are crucial. In addition, health care providers should consider that 46,XY patients carry a risk of developing gonadal tumors, requiring gonadectomy. The current patient had undergone gonadectomy before she was admitted to our department.

The relationship between the physiology of hormone systems and psychiatric signs and symptoms is considerably complex. DHEA and pregnenolone are two important norestrogens, which can be transformed into their sulfate forms. These forms can cause significant changes in behavior. In the current patient, low DHEA levels were associated with recurrent depression symptoms, which required antidepressant treatment.

Unlike other forms of CAH, the diagnosis of 17-OHD is generally late, often delayed until adulthood. Hypokalemic hypertension is the main component of 17-OHD, but it is not seen in 10% - 15% of patients. Therefore, diagnosis may be difficult and delayed. When there is no hypertension or hypokalemia, low/near low levels of potassium and high progesterone levels should are representative of 17-OHD. In late-diagnosed cases, it is known that renovascular changes secondary to chronic hypertension may cause permanent hypertension, even if the ACTH level is adequately suppressed by hydrocortisone therapy and the DOC level is brought to the normal limits. Spironolactone and calcium channel blockers may be used in these patients. In addition, psychological problems, osteoporosis, and gender selection are other important problems in the late diagnosis of these patients.

In this case report, it was interesting that the patients were raised as girls, one with 46, XX, and the other with 46, XY karyotype from the same family.

Although they had the same deletion, they had different clinical and laboratory findings. One patient responded (with early diagnosis) well to the treatment, whereas the other one (with late diagnosis) did not. In the first case, pubic hair progressed to Tanner stage 2 after treatment, which is also an interesting and unexpected finding for 17-OHD deficiency. Also, it was interesting that myelipoma can rarely be seen in this form of congenital adrenal hyperplasia.

Early diagnosis and treatment enable the induction of puberty at the appropriate time and can prevent hypertension, osteoporosis, and psychological problems.

Footnotes

Conflict of Interests: The authors declare that they have no competing interests

Ethical Approval: We received written consent from the parents and ethical approval from the Ankara Dışkapı Children Hematology-Oncology Hospital Ethic Committee (2019-147).

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Informed Consent: We received the written consent form.

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