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Case Report

Seventeen Alpha-Hydroxylase Deficiency Associated with Absent Gonads and Myelolipoma: A Case Report and Review of Literature

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Abstract

Congenital adrenal hyperplasia comprises a group of disorders resulting from defects in enzymes required for the synthesis of cortisol. The clinical presentation depends on the specific enzyme defect. We report a rare case of congenital adrenal hyperplasia due to 17 alpha-hydroxylase deficiency. A 26-year-old female patient referred with hypertension and hypokalemia. She also had primary amenorrhea and lack of sexual development. The karyotype was 46, XY. Hormonal evaluation showed low serum levels of all steroid hormones, requiring alpha-hydroxylation, which included cortisol, 17 alpha-hydroxy progesterone, dehydroepiandrosterone sulfate, estradiol, and testosterone. The levels of adrenocorticotropic, follicle-stimulating, and luteinizing hormones were high. Radiological and surgical investigations failed to show a gonad. She also had a large myelolipoma. Treatment was commenced with low-dose dexamethasone and conjugated estrogen. Her hypertension and hypokalemia were resolved. The myelolipoma was removed by laparoscopy due to pain and sensation of heaviness. Our review of literature revealed that a combination of this disorder with either agonadism or myelolipoma is very rare and that only 2 previous cases have been reported for each entity.

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Keywords ● Steroid 17-alpha-hydroxylase ● Adrenal hyperplasia-congenital ● Male pseudohermaphroditism ● Gonads ● Myelolipoma

What's Known

- Myelolipoma can occur in common forms of congenital adrenal hyperplasia such as 21 hydroxylase deficiency.
- Patients with 17 alpha-hydroxylase deficiency have gonads compatible with their karyotypes.

What's New

- We reported myelolipoma in a patient with 17 alpha-hydroxylase deficiency.
- Our patient, with 46XY karyotype and female phenotype, had no gonads and we concluded that his testes had undergone severe atrophy early in embryonic life.

Introduction

Seventeen alpha-hydroxylase deficiency is a rare form of congenital adrenal hyperplasia (CAH), with about 150 cases reported in the world literature.[1] In this disorder, abnormal steroid metabolism leads to impaired sexual development, hypertension, and hypokalemia.[2] The coexistence of either agonadism or myelolipoma with 17 alpha-hydroxylase deficiency is very rare, and there are only 2 previous reported cases for each entity.[3-6]

Case Report

Informed written consent was obtained from the patient for reporting this case. A 26-year-old female patient was referred

to Nemazee Hospital for an evaluation of hypertension and hypokalemia. She had been relatively well up to 2 months prior to admission, when she developed weakness and headache. In her past history, she had been found to be hypertensive at the age of 18 years and she had been intermittently treated with antihypertensive drugs. She also had primary amenorrhea. There was no history of hernia surgery. Her parents were cousins. On physical examination, she was tall and thin (173 cm in height and 58 kg in weight), with a blood pressure of 170/120 mm Hg. There was no breast development. The skin was mildly hyperpigmented, and pubic, axillary, and body hair was absent. The genitalia were female with mild cliteromegaly and hypospadias. The vagina was shallow.

Laboratory investigations revealed normal levels for hemoglobin and blood cell counts and renal and liver function tests. Calcium, phosphate, and thyroid function tests were also normal. Serum sodium was 138 meq/L and potassium was 2.6 meq/L.

Because of her clinical findings, disorders of adrenal metabolism were suspected. Samples were taken for hormonal evaluation, and amlodipine (10 mg/d) and spironolactone (100 mg/d) were prescribed to control blood pressure and hypokalemia. The hormonal evaluation results are depicted in table 1. The hormone measurements were done by electrochemiluminescence assay (ELECSYS 2010, Roche, Germany) and enzyme-linked fluorescent assay (VIDAS system, BioMérieux, France).

Karyotype was done, and the result was 46, XY. Computed tomography (CT) scan of the abdomen showed bilateral enlarged adrenals, 6.5 cm on the left side and 3 cm on the right side (figure 1). Because of the patient's karyotype result, extensive search was done to detect ectopic testes. On sonography and magnetic resonance imaging of the pelvis, there was no uterus, adnexa, and gonads. Sonography of the inguinal area and labia demonstrated no mass or abnormal tissue. She was treated as a case of 17 alpha-hydroxylase deficiency with 0.5 mg of dexamethasone per day and her blood pressure and potassium became normal without use of hypertensive drugs. Her dexamethasone dose was later decreased to 0.25 mg/d. Conjugated estrogen (0.625 mg/d) was also started. One year later, she had Tanner stage 1 breast development. Because of asymmetric adrenal enlargement and left flank pain and continued sensation of heaviness, left-side laparoscopic adrenalectomy was performed and pathologic study showed myelolipoma and adrenal hyperplasia (figure 2). On pelvic laparoscopy, there was no ectopic testis tissue.

Discussion

CAH is caused by genetic defects in the enzymes that are required for the synthesis of cortisol. They are inherited as autosomal recessive disorders. Low levels of cortisol lead to a lack of negative feedback at the level of the hypothalamus and increased secretion of the adrenocorticotropin hormone (ACTH), which stimulates adrenal hyperplasia and the production of steroid precursors proximal to defective enzyme.[2] Seventeen alpha-hydroxylase deficiency is due to mutations in the *CYP 17 A1* gene, located on chromosome 10.[7] This enzyme is essential for the production of cortisol, androgens, and estrogen. In patients with this disorder, the steroid precursors are converted to progesterone and then to products with mineralocorticoid activity such as 11-deoxycorticosterone and

Table 1: Results of hormonal evaluation

	Patient's value	Female reference range (follicular phase)
Luteinizing hormone	56	1.9–9.2 U/L
Follicle-stimulating hormone	145	3.5–9.2 U/L
Estradiol	<9.0	18–147 pg/mL
Testosterone	<0.02	0.084–0.481 ng/mL
Dehydroepiandrosterone sulfate	<2.5	98.8–340 µg/dL
Progesterone	5.8	0.25–0.54 ng/mL
17-OH progesterone	<10	20–100 ng/dL
Cortisol	0.9	5.4–28.7 µg/dL
Adrenocorticotropic hormone	185	6–76 pg/mL
Deoxycorticosterone	54	2–19 ng/dL
Aldosterone (supine)	0.5	2–9 ng/dL
Plasma renin activity (supine)	0.1	0.2–1.6 ng/mL/h
Anti-Müllerian hormone	<0.2	For female: 1–10 ng/mL For male: 0.7–20 ng/mL

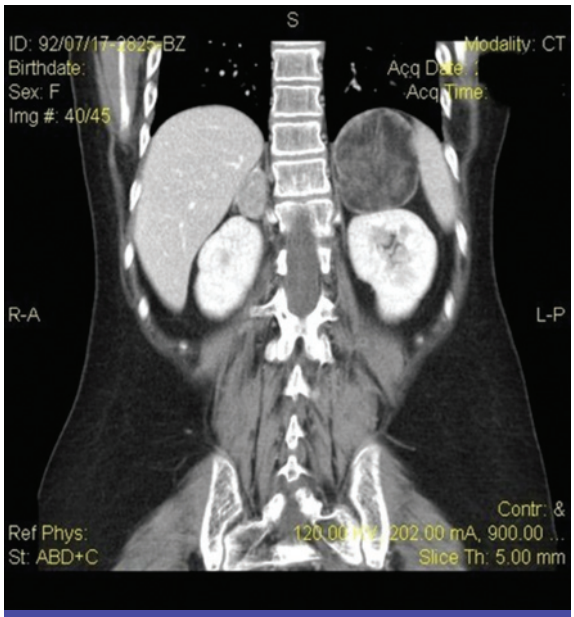

Figure 1: Coronal computed tomography scan of the abdomen shows bilateral enlarged adrenals: the left adrenal is 6.5 cm in size and is heterogeneous with fat-containing components.

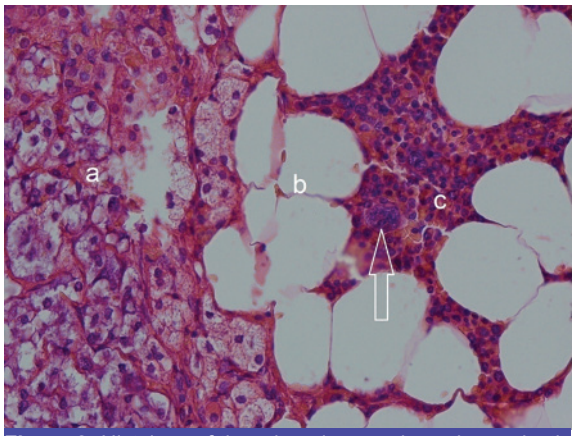

Figure 2: Histology of the adrenal mass shows hyperplastic adrenal tissue (a), adipose tissue (b), and bone marrow cells (c), including megakaryocytes (pointer), consistent with the diagnosis of myelolipoma (H&E stain).

corticosterone.[7] High levels of mineralocorticoids cause hypertension and hypokalemia, which were the main presentation of our case.

Our patient had the typical hormonal profile of 17alpha-hydroxylase deficiency. Seventeen alpha-hydroxylase is present in gonads and adrenals; consequently, its defect, as was the case in our patient, results in low levels or absence of all sex hormones, with a subsequent increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[7,8] In 46,XY individuals, a lack of testosterone gives rise to male pseudohermaphroditism and these individuals grow up as female.[8] In our patient, cortisol was low and ACTH was high. Chiming in with the other reported cases, our patient had no symptoms of cortisol deficiency. This is due to weak glucocorticoid activity of corticosterone, which at high levels prevents the effects of cortisol deficiency.[9] The progesterone level was high, but 17 hydroxy progesterone was undetectable because of the absence of 17 hydroxylase activity. Rennin and aldosterone were suppressed as a result of volume expansion caused by high levels of mineralocorticoid products.[9]

Karyotype was 46,XY in our patient; nevertheless, during the embryonic period, a low level of testosterone had led to the agenesis of the internal male genital organs such as the prostate and seminal vesicles and the absence of the masculinization of the external genitalia. Typical 46,XY patients have testes in the pelvis, inguinal area, or labia.[8] The unique feature of our patient, however, was the absence of testes in the above sites. Anti-Müllerian hormone (AMH) was also undetectable, supporting the absence of viable testis tissue and sertoli cells. Two other such patients with 17 alpha-hydroxylase deficiency, 46,XY karyotype, and absent gonads have been reported in the literature.[3,4] Malcolm et al.[3] described a 23-year-old female patient with 17 alpha-hydroxylase deficiency and 46,XY karyotype and absent gonads. Nonetheless, by comparison with our patient, theirs had a small uterus. Tvedegaard et al.[4] reported a similar case with complete gonadal agenesis and absent adnexa. These authors had no clear explanation for this presentation. Our patient had no Müllerian-derived organs such as uterus and fallopian tubes, which implies that during early embryonic life, there were viable testicles to produce AMH and cause the regression of the Müllerian-system and that the testes regressed later for unknown reasons. Mild cliteromegaly and hypospadias also show exposure to low levels of androgens in the embryonic period. Torsion, ischemia, and subsequent necrosis can been postulated as the cause of testes regression in this patient.[10]

Another feature of our patient was the presence of a large myelolipoma in her left adrenal. Myelolipomas are rare benign tumors consisting of mature adipose tissue and bone marrow cells of myeloid, erythroid, and megakaryocytic lines.[11] They are usually found incidentally in the adrenals but sometimes are associated with endocrinopathies such as Cushing's disease and adrenal adenoma. The association between myelolipoma and CAH is rare, with only about 30 previous cases having been reported in the literature. Most of these cases were 21 hydroxylase deficient, and only 2previous cases of 17 hydroxylase deficiency

with a myelolipoma have been previously reported.[5,6] As was the case in our patient, in both of those previously reported cases, the tumor was unilateral. The etiology of myelolipoma in CAH is not clear, but exposure to high ACTH and other adrenal growth factors may play a role.[11]

The appropriate treatment of patients with 17 alpha-hydroxylase deficiency, as in other variants of CAH, is glucocorticoid replacement therapy. Small doses of dexamethasone or prednisolone decrease ACTH and subsequently the11-deoxycorticosterone level declines, which normalizes blood pressure and electrolyte imbalance.[7] Our patient had a favorable response to low-dose dexamethasone. Sex hormone replacement therapy is also needed to preserve bone mass and stimulate the development of secondary sexual characteristics. In 46,XX patients, cyclic estrogen and progesterone therapy is used to prevent endometrial hyperplasia. In 46,XX patients with pseudohermaphroditism, if the patient desires to be male, androgen replacement therapy and genital reconstructive surgery should be considered. In those who are reared as female, treatment with estrogen alone is recommended.[7] Our patient was maintained on conjugated estrogen (0.625 mg/d), and the response was favorable.

Conclusion

In contrast to other forms of CAH, the diagnosis of 17 alpha-hydroxylase deficiency is usually delayed to adulthood. As was illustrated in our patient, young hypertensive patients with disorders of puberty should be evaluated for 17alpha-hydroxylase deficiency. In these patients, a measurement of plasma cortisol can be helpful to evaluate the presence of a major disorder of steroid synthesis.

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Conflict of Interest: None declared.

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