Case Report

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Multidisciplinary team management of 46,XY 17α-hydroxylase deficiency: a case report and literature review

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Abstract

Background: We report here a case study of 17α-hydroxylase deficiency in a phenotypic girl with male karyotype (46,XY). We also review the relevant literature to deepen our understanding of the disease, reduce the rate of missed diagnosis, and emphasize that holistic management of this disease requires collaborative multidisciplinary teamwork.

Case presentation: A 14-year-old patient with a female phenotype visited the endocrinology department because of hypertension. The patient had primary amenorrhea and lacked secondary sexual characteristics. Initial laboratory evaluation revealed normal levels of electrolytes, a hypergonadotropic hypogonadal state with high progesterone and low testosterone levels, and a 46,XY karyotype. She was referred to the urology department for gonadectomy and transferred to the gynecological endocrine clinic. On the basis of the patient's medical history and genetic testing results, a diagnosis of 46,XY 17α-hydroxylase deficiency was made. The patient was provided with glucocorticoids, estrogens, metformin, and psychological support.

Conclusions: Patients with 17α-hydroxylase deficiency, a rare cause of congenital adrenal hyperplasia, should be treated by a multidisciplinary team. Relevant experts from different disciplines should set up a systematic and comprehensive individualized management plan to optimize the physical and mental health and quality of life of affected patients.

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Introduction

17α-Hydroxylase deficiency (17OHD) is a rare autosomal recessive disorder caused by mutations in the *CYP17A1* (cytochrome P450, family 17, subfamily A, polypeptide 1) gene with an estimated incidence of 1 in 50,000.[1] 17OHD affects both adrenal and gonadal function,[2] resulting in disorders in the synthesis and secretion of corticosteroids, glucocorticoids, and sex hormones.[1,3] Genotypic boys (46,XY) demonstrate impaired virilization, sexual infantilism, and absence of pubertal development because of androgen insufficiency.[4] With the rapid advances of biomedical science in recent years, increasing evidence suggests that a multidisciplinary team (MDT) is required for the diagnosis and management of 17OHD,[5–7] including clinicians in pediatrics, gynecology, urology, endocrinology, orthopedics, plastic surgery, and psychosocial treatment. Here, we summarize the diagnosis and treatment of a patient with 17OHD, review the relevant literature, and emphasize the importance of MDT.

Case report

A 14-year-old girl presented to the Endocrinology Department of the First Affiliated Hospital of Xi'an Jiaotong University with palpitations, chest tightness, and shortness of breath that developed during military training. The patient was an apparently normal girl when she was delivered at full-term. Her parents are non-consanguineous, and her mother had no history of taking medications during pregnancy that could cause fetal malformations. There was no family history of chronic illnesses, including hypertension.

Physical examination showed that the patient was 171 cm tall with a weight of 75 kg and a body mass index (BMI) of 25.65 kg/m^2. Her blood pressure, pulse, and respiratory rate were 160/100 mmHg, 74 beats/minute, and 18 breaths/minute, respectively.

The patient had Tanner stage II breast development and female infantile external genitalia with a hymenal ring and vaginal dimples. Results of laboratory evaluations are given in Table 1. Laboratory analysis revealed normal levels of potassium and aldosterone. Plasma adrenocorticotropic hormone (ACTH) was markedly elevated, cortisol was at the lower limit of normal, and levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and progesterone were increased. Levels of testosterone, dehydroepiandrosterone sulfate (DHEAS), and estradiol were substantially decreased. Dual-energy X-ray absorptiometry indicated that the patient had low bone mass (Z score: −3.7).

Trans-abdominal pelvic ultrasound revealed the cryptorchidism in the bilateral inguinal region and the absence of a uterus and ovaries. A computed tomography scan of the adrenal glands showed thickening of the left adrenal junction (Figure 1).

After detailed physical examination and laboratory evaluations, diagnoses of renal hypertension, primary aldosteronism,

Table 1. Laboratory analyses in our patient with 17α-hydroxylase deficiency.

Characteristic	Value	Reference range
Potassium (mmol/L)	4.29 (N)	3.5–5.3
Aldosterone (pg/mL)	156.5 (N)	65.2–295.7
ACTH (pg/mL)	259.6 (↑↑)	7.20–63.30
Cortisol (μg/dL)	5.05	5–28
FSH (mIU/mL)	45.430 (↑)	Follicular phase: 3.5–12.5 Ovulatory phase: 4.7–21.5 Luteal phase: 1.7–7.7 Postmenopausal: 25.8–134.8
LH (mIU/mL)	45.430 (↑)	Follicular phase: 2.4–12.6 Ovulatory phase: 14.0–95.6 Luteal phase: 1.0–11.4 Postmenopausal: 7.7–58.5
Progesterone (nmol/L)	21.23 (↑)	Follicular phase: 0.181–2.84 Ovulatory phase: 0.385–38.1 Luteal phase: 5.82–75.9 Postmenopausal: <0.159–0.4
Estrogen (pmol/L)	88.5 (↓)	Follicular phase: 45.4–854 Ovulatory phase: 151–1461 Luteal phase: 81.9–1251 Postmenopausal: <18.4–505
PRL (ng/mL)	11.16 (N)	4.79–23.3
Testosterone (nmol/L)	0.663 (↓)	Female (20 to 49 years): 0.29–1.67 Male (13 to 17 years): 0.98–38.5
DHEAS (μmol/L)	0.608 (↓)	0.92–7.6
$VITD_3$-T (ng/mL)	8.4 (↓)	20–40
Karyotype analysis	46,XY	

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; DHEAS, dehydroepiandrosterone sulfate; $VITD_3$-T, total 25-hydroxyvitamin D_3; N, normal levels; ↓, below normal; ↑, above normal.

pheochromocytoma, Cushing's syndrome, hyperthyroidism, and pseudoaldosteronism (Liddle syndrome) were excluded, and the patient received treatment for hypertension of nifedipine controlled-release tablets 30 mg three times per day.

Because the karyotype of the patient was 46,XY and cryptorchidism was found, the patient was referred to the urology department for bilateral cryptorchidectomy with a diagnosis of "abnormal sexual differentiation, grade 3 hypertension (low risk)." After surgery, she attended the gynecological endocrine clinic for sex hormone replacement therapy.

Considering the high levels of plasma FSH, LH, and progesterone; low levels of estradiol, testosterone, and DHEAS; the physical examination results; and the history of hypertension, a diagnosis of 17OHD was made. Genetic testing results showed a heterozygous mutation of *CYP17A1* gene: c.1169C>G (p. Thr390Arg), c.985_987delTACinsAA (p. Tyr329fs). Because her BMI was 25.65 kg/m^2, a glucose tolerance test and insulin release test were performed, and the results indicated hyperinsulinemia. Therefore, the final diagnosis was (1) congenital adrenocortical hyperplasia 46,XY 17OHD, (2)

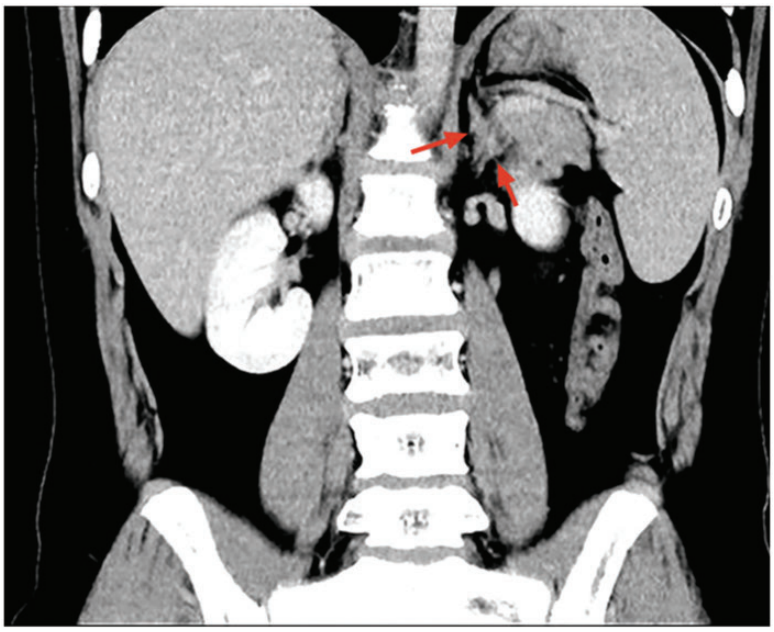

Figure 1. Abdominal enhanced computed tomography scan showed thickening of the left adrenal junction and the medial limb bulging outward (red arrows).

hyperinsulinemia, (3) vitamin D deficiency, and (4) low bone mass.

Following consultation with the patient and her parents, the decision was made to maintain the female gender identity. The patient received estrogen replacement therapy to promote development of secondary sexual characteristics, prevent osteoporosis, and improve long-term outcomes.

Under the guidance of endocrinologists, oral hydrocortisone was prescribed to inhibit abnormally elevated ACTH, reduce aldosterone secretion, and decrease blood pressure (hydrocortisone: 20 mg and 10 mg at 8:00 am and 4:00 pm, respectively). Calcium carbonate D_3 was given to supplement vitamin D and calcium levels. The patient was regularly followed by the gynecology, endocrinology, and orthopedics departments. One month later, the hydrocortisone dosage was reduced (10 mg at 8:00 am and 4:00 pm).

Discussion

Diagnosis of 17OHD

17OHD is a rare condition that accounts for approximately 1% of cases of congenital adrenal hyperplasia (CAH).[9] The microsomal cytochrome P450 enzyme encoded by *CYP17A1* is a key enzyme in the synthesis of gonadal steroids and adrenocortical hormones.[10] *CYP17A1* gene deficiency affects the enzyme's activity, leading to disorders in the synthesis of corticosteroids, estrogens, and testosterone.[3] Decreased cortisol secretion increases production of ACTH and adrenocortical hyperplasia,[1] whereas accumulation of pregnenolone and progesterone results in the increased transformation of saline corticosteroids as well as high plasma progesterone levels.[11] This state of mineralocorticoid excess is classically characterized by different degrees of hypertension and hypokalemia and a low or

Table 2. Key points of the differential diagnosis among complete androgen insensitivity syndrome (CAIS), 46,XY gonadal hypoplasia, and 17OHD.

Characteristic	CAIS	46,XY gonadal hypoplasia	46,XY 17α-hydroxylase deficiency (17OHD)
Primary amenorrhea	+	+	+
Breast development	+	−	−
Pubis	−	−	−
External genitalia	Female	Female	Female
Vaginal	Blind-ending	+	Blind-ending or vaginal dimple
Uterine	−	+	−
Artificial menstrual cycle	−	+	−
Gonads	Testes (normal size)	Testes (streak gonads)	Testes (hypoplasia, small and/or ectopic)
Karyotype	46,XY	46,XY	46,XY
Testosterone	N	↓	↓
Estrogen	N	↓	↓
Progesterone	N	↓	↑↑
Hypertension	−	−	+ or normotensive
Hypokalemia	−	−	+ or normokalemic

+, positive/presence, −, negative/absence, N, normal levels; ↓, below normal, ↑, above normal.

subnormal aldosterone concentration.[4] In patients with 46,XY 17OHD, normal secretion of anti-Müllerian hormone in the embryonic stage causes regression of the Müllerian ducts (fallopian tubes, uterus, and upper third of vagina).[12] The internal genitalia are hypoplastic testes, but the external genitalia are infantile female or ambiguous due to the absence of androgen, and no secondary sexual signs or typical sexual development occurs during the pubertal years.[13]

The phenotypic severity of 17OHD depends primarily on whether the activities of enzymes are completely or partially lost, which depends on the type and localization of the mutation in the *CYP17A1* gene.[3] However, remarkable variation in the severity of the clinical manifestation of the same mutation has been noted.[3,12,14,15] In recent years, some patients with incomplete 17OHD have been found to be normokalemic and normotensive, with breast development and ambiguous external genitalia.[16,17] Because of the heterogeneity of the clinical manifestations of 17OHD, the incidence of misdiagnosis or missed diagnosis early in the process is very high.[17] For example, primary amenorrhea in adolescents is a common reason for a patient to present to a department of gynecology. If laboratory evaluation of sex hormones suggests hypergonadotropic amenorrhea, then the differential diagnosis includes 46,XY gonadal hypoplasia and complete androgen insensitivity syndrome (Table 2). Persistent hyperprogesterone is a typical characteristic of CAH.[11] However, some doctors believe that these patients do not ovulate and thus the doctors do not test progesterone levels when primary hypergonadotropic amenorrhea is identified in clinical practice. It is also possible that progesterone levels were measured but the doctors disregarded the results, leading to the missed diagnosis.

With the rapid development of genetic and molecular diagnostic technology, as well as the highly variable clinical and

biochemical presentations of this disorder, genetic testing plays a critical role in confirming the diagnosis. Through April 2019, 137 different mutations in *CYP17A1* had been identified in the Human Gene Mutation Database (http://www.hgmd.org/), including missense or nonsense mutations; splicing and regulatory mutations, small insertions, deletions, and indels; gross deletions; and complex rearrangements. Our patient showed a heterozygous mutation in *CYP17A1*: T390R and Y329fs; the T390R mutation was first reported by Han et al.[18] in a patient with atypical 17OHD, and the Y329fs mutation is reported to be one of the most common mutations of *CYP17A1* in China.[19]

Multidisciplinary management of 17OHD

An important issue in the treatment of 17OHD in genotypic boys (46,XY) is the appropriate time of gonadectomy. Early reports have shown an increased risk of germ cell tumors (10% to 30%) in phenotypic girls with a Y chromosome or Y-derived sequences, and gonadectomy is recommended as soon as possible after diagnosis.[20] Recently, it has become clear that the risk of cancer in patients with disorders of sex development (DSD) depends on multiple factors, including the subtype of DSD, age, diagnostic tools (karyotyping, genetic analysis, or hormone testing), gonadal location, histology, and diagnostic markers (such as testis-specific protein Y-linked region).[21–23] Thus, the decision to recommend gonadectomy should be individualized to the patient and should be made by a specialized MDT including, at minimum, geneticists, endocrinologists, behavioral health specialists, and urologists.[24]

Currently, the data regarding gonadal malignancy risk for cases of 17OHD are limited. Brooke et al.[14] reported a malignant mixed germ cell tumor originating from a yolk sac element in a 17-year-old girl with 17OHD. A retrospective study conducted by Jiang et al.[13] in China in 2016 analyzed clinical data of 30 patients with 46,XY 17OHD. Two patients had tumors: a 16-year-old patient with a Leydig cell tumor and a 17-year-old patient with a Sertoli cell tumor; both cases were confirmed by histopathology. The authors recommended that early diagnosis and timely gonadectomy are critical to prevent gonadal malignancy. Considering that the phenotype and gender of our patient were female, a bilateral gonadectomy was performed when cryptorchidism was observed.

The management of mental health and psychosocial problems associated with DSDs is another focus of clinical researchers. Our patient showed introversion and feelings of inferiority with impaired self-image and self-esteem at her first visit to our department. Through transparent communication and discussion with the patient and her family, they were able to fully understand what 17OHD is, why it happens, and what treatment options are available. We offered careful counseling about sexual activity and future chances of fertility for the patient. The patient and her parents agreed to maintain the female gender identity. The Consensus Statement developed by the European Cooperation in Science and Technology (COST) in (2018)[7] advocated that clear and consistent communication improves confidence in the medical team and enables future joint decision-making and treatment compliance.

According to the COST Consensus Statement,[7] longitudinal holistic care for adults requires a wide range of disciplines. Decreased bone mineral density has been observed in up to 70% of female patients with CAH 30 years of age or older.[25] Our patient showed declining bone mineral density and low levels of estrogen and vitamin D_3. Considering that lifelong treatment with glucocorticoids will lead to further bone loss and that the patient lacked a

uterus, she was administered estrogen, vitamin D, and calcium to promote the development of secondary sexual characteristics and improve current cardiovascular and bone health, as well as long-term outcomes. Furthermore, the patient had developed obesity and insulin resistance. Obesity is contributes to the development of hypertension and cardiovascular diseases,[26] and increased blood pressure is an intrinsic feature of 17OHD. Therefore, our nutritional department prescribed metformin (500 mg, 3 times per day) and designed a weight loss program to alleviate metabolic disturbances.

In conclusion, we have summarized the main aspects of 17OHD through a detailed description of the diagnosis and treatment process in a patient. Because this disease is relatively rare, we recommend an MDT to reduce the chance of a missed diagnosis, set up a systematic and comprehensive individualized long-term management plan, and optimize the physical and mental health and quality of life of affected patients.

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Ethics statement

The study complied with the CARE guidelines: consensus-based clinical case reporting guideline development.[8] We obtained written consent for treatment of the patient, and we have deidentified all patient details in this report. Ethical board approval was deemed unnecessary.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

YZ analyzed and interpreted the patient data and drafted the final manuscript; PPS, XX, and QRL contributed to gathering patient data; SLL reviewed the final manuscript and was a major contributor in writing the manuscript. All the authors read and approved the final manuscript.

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