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Two cases of sisters-patients with congenital adrenal hyperplasia-21-hydroxylase deficiency.

Zou Fang, Lei Shuihong, Hu Lei, Shen Yunfeng, Lai Xiaoyang*

Endocrine Metabolism Department, the Second Affiliated Hospital of Nanchang University, PR China

Abstract

This is one case report that about two cases of sisters-patients with congenital adrenal hyperplasia-21-hydroxylase deficiency. The 2 patients in this group had significant masculine performance of women, without hypertension and electrolyte imbalance. The specific diagnostic index of 17-OHP was significantly increased, meanwhile testosterone, ACTH and 17 ketone steroids were significantly higher than the normal level. Adrenal CT showed bilateral adrenal hyperplasia, diagnosed as the simple masculine type in 2l-hydroxylase deficiency.

Keywords: Sisters-patients, Congenital adrenal hyperplasia-21-hydroxylase deficiency.

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Introduction

Case 1

The patient was 14 years old. After birth, she had genital abnormalities manifested as the hypertrophy labia and clitoris, raised as a girl. At the age of 4, her pubic hair was in growth, accompanied with gradually enlarged clitoris and labia, which was in rapid growth before 8 years old. After that, the growth stagnated. She received "vulva plastic surgery" in a Shanghai hospital (specific unknown) in 9 years old, so far no breast developed, no menstrual cramps. She was in full-term delivery. Her mother had no obvious infection and no drug history of androgen during pregnancy. The parents are close relatives and show normal.

Physical examination

The blood pressure and the stature of her were 110/80 mmHg and 137 cm, respectively. She was in small size, masculine and systemic skin had mild hyperpigmentation, especially in areola and genital; the body hair increased, the hair grew along the median line of the lower abdomen, inner thighs and around the areola. The breast had no development, and limbs were muscular. Genital examination indicated the clitoris length was about 0.8 cm, the small and large labias were visible, but there was no vaginal mouth, and pubic hair was much and dense. Auxiliary examinations: she had normal serum electrolytes, Follicle-Stimulating Hormone (FSH) of 4.21 mU/L (2.5-10), Luteinizing Hormone (LH) of 5.25 mU/L (4.9-13), estradiol (E2) of 45.39 ng/ml (19.5-144.2), pregnancy Ketone (P) of 11.77 ng/ml (0.15-1.4), Testosterone (T) of 559 ng/ml (14-76), 17-hydroxyprogesterone (17 OHP) of 32.69 ng/ml (0.07-1.53), Dehydroisoandrosterone (DHEA) of 433 μg/(0.3-7.5), androstenedione>10 ng/ml (0.3-3.5), Adrenocorticotropic Hormone (ACTH) of 350 ng/L (12-78), cortisol at 8 in the morning of 4.77 μg/dL (4.3-22.4), urinary 17 hydroxysteroid (17-OH) of 13.45 μmol/24 h (5.5-22.0), urinary 17-hydroxy (17-KS) of 104.94 μmol/24 h (21-49); chromosome karyotype analysis of the peripheral blood: 46, XX. Gynecological ultrasound showed she may have immature uterus, the volume of bilateral ovarian was too small. Double adrenal gland CT scan showed congenital bilateral adrenal hyperplasia, diagnosed as congenital adrenal hyperplasia and 2l-hydroxylase deficiency.

Case 2

The patient was 20 years old. After birth, she had genital abnormalities manifested as the hypertrophy labia and clitoris, raised as a girl. At the age of 5, her pubic hair was in growth, accompanied with gradually enlarged clitoris and labia, which was in rapid growth before 8 years old. After that, the growth stagnated. So far no breast developed any menstrual cramps. She was in full-term delivery. Her mother had no obvious infection and no drug history of androgen during pregnancy. The parents are close relatives and show normal.

Physical examination

The blood pressure and the stature of her were 120/80 mmHg and 142 cm, respectively. She was in small size and masculine; the body hair was thick. The breast had no development, and limbs were muscular. Genital examination indicated the clitoris length was about 1.5 cm, the small and large labias were visible, but there was no vaginal mouth, and pubic hair was much and dense. Auxiliary examination: she had normal serum electrolytes, Follicle-Stimulating Hormone (FSH) of 4.71 mU/L (2.5-10), Luteinizing Hormone (LH) of 8.54 mU/L (4.9-13), Estradiol (E2) of 48.05 ng/ml (19.5-144.2),

pregnancy Ketone (P) of 12.49 ng/ml (0.15-1.4), Testosterone (T) of 358 ng/ml (14-76), 17-hydroxyprogesterone (17 OHP) of 32.35 ng/ml (0.07-1.53), Dehydroepiandrosterone (DHEA) of 829 μg/dl (35-430), androstenedione>10 ng/ml (0.3-3.5), Adrenocorticotropic Hormone (ACTH) of 252 ng/L (12-78), cortisol at 8 in the morning of 7.74 μg/dL (4.3-22.4), urinary 17 hydroxysteroid (17-OH) of 7.56 μmol/24 h (5.5-22.0), urinary 17-hydroxy ketone steroid (17-KS) of 62.93 μmol/24 h (21-49) (Table 1); Chromosomal karyotype analysis of peripheral blood: 46, XX. Gynecological ultrasound showed she may have immature uterus, bilateral ovarian were normal. Double adrenal gland CT scan showed congenital bilateral adrenal hyperplasia, diagnosed as congenital adrenal hyperplasia and 2l-hydroxylase deficiency.

Table 1. *The blood test value of cases 1 and 2.*

	FSH	LH	E2	P	T	17 OHP	DHEA	ACTH
Case 1	4.21	5.25	45.39	11.77	559	32.69	433	252
Case 2	4.71	8.54	48.5	12.49	358	32.35	829	252

Treatment

0.75 mg dexamethasone was administrated at zero o'clock per night. Because of economic shortage, the older sister was undergoing genital plastic surgery, the treatment effect was still in followed-up.

Discussion

Congenital Adrenal Hyperplasia (CAH) is caused by congenital defects of one or more adrenal cortical hormone biosynthesis enzymes. The enzymes involved in the synthesis are cholesterol 20, 22 lyase, 17α-hydroxylase, 3 β-HSD, 21 α-hydroxylase, 11 β-hydroxylase. The most common in clinic is 21 α-hydroxylase deficiency (21 OHD), accounting for 90%-95%; Followed is 11 β-hydroxylase deficiency for 5% to 8%; others such as 3 β-hydroxy alcohol dehydrogenase deficiency, 17 α-hydroxylase deficiency, cholesterol carbon chain enzyme deficiency rarely occurs. The role of 21 α-hydroxylase is to catalyse progesterone into Deoxy Corticosterone (DOC) and 17-Hydroxyprogesterone (17-OHP) into 11-deoxy cortisol respectively in the adrenal cortex reticular and fascicular band, respectively. These two substances are essential precursor substance for the synthesis of aldosterone and cortisol from adrenal. The deficiency or inactivation of 21 α-hydroxylase resulted in decreased cortisol synthesis and removal of the ACTH inhibition. ACTH compensatory secretion will increase to promote bilateral adrenal hyperplasia. Progesterone, the precursor of 21 α-hydroxylase enzymatic reaction, and 17-OHP accumulated and conversed to androgen synthesis pathway. Reduced cortisol and aldosterone, along with increased androstenedione and testosterone contributed to adrenocortical insufficiency and abnormalities of sexual differentiation (male precocity and female masculine). According to the degree of 21 α-hydroxylase deficiency, it can be divided into the salt-losing type, simple masculine type and non-classic type. Due to the condition of salt-losing type is severe, more are dead in childhood. Simple masculine type is more common clinically [1].

The 2 patients in this group had significant masculine performance of women, without hypertension and electrolyte imbalance. The specific diagnostic index of 17-OHP was significantly increased, meanwhile testosterone, ACTH and 17 ketone steroids were significantly higher than the normal level. Adrenal CT showed adrenal hyperplasia, diagnosed as the simple masculine type in 2l-hydroxylase deficiency. 20-year-old sister is only 142 cm tall, 14-year-old sister is 137 cm, while they were in rapid growth before 8 years old. This is because patients with 21-OHD simple masculinization have in long-term continuous hyperandrogenism to accelerate early growth in children. Usually they are significantly higher than normal children with the same age, with accelerated bone maturation, ahead bone age and advanced epiphyseal fusion. In early childhood, they were taller than the same age children, the final height is not as tall as normal adults.

Congenital adrenal hyperplasia is an autosomal recessive inheritance, and has high incidence in the progeny of the offspring of marriage. The parents of this group of patients are in consanguineous marriage. We searched 1988-2014 literature with Wanfang database, there are a total of 13 cases reports for familial congenital adrenal hyperplasia cases in China [2-14]. Janjanin abroad in 2007 reported 5 patients with 21-hydroxylase deficiency of three generations were a grandmother, parents and two children [15]. The incidence of this disease is low, not common in clinic. So as to improve the diagnosis of this disease, we must first improve clinicians the understanding of the disease and emphasize a comprehensive physical examination. Females who had female pseudohermaphroditism post-natal, adolescent height was significantly higher than the same age children, while the adult height was lower than normal, had no developed adolescent female secondary sexual characteristics, amenorrhea, voice thick, Adam's apple, thick body hair, male pubic hair distribution, muscular, pigmentation of skin and genitalia, should be considered as CAH; secondly, emphasize biochemical tests and related hormonal and imaging studies; In conditional areas, neonatal screening for CAH should be carried out, screening can make about 70% of children with 21 α-hydroxylation enzyme deficiency before clinical symptoms obtain early diagnosis and treatment. Two patients in this group were born in the following hospitals in the county and had no new-born screening, so vigorously popularize new-born screening is useful for early detection of congenital diseases and early treatment. In addition, to avoid consanguineous marriage, if the parents are close relatives, the prenatal screening for CAH should be strengthened. In current, foreigners take the villus in early pregnancy (9 to 11 weeks) to extract DNA or culture amniotic fluid cells from 16 to 20 pregnant weeks for DNA extraction, PCR dot blot and other molecular biology techniques were used for genetic diagnosis

[16]. Prenatal diagnosis and early intervention (in the first 3 to 10 weeks of pregnancy) can make 21-hydroxylase deficiency become the first disease to be in prenatal therapy in clinic.

Early application of glucocorticoid inhibitory replacement therapy is a common treatment for various types of congenital adrenal hyperplasia, and adolescent pre-treatment effect is significant. The suitable amount of exogenous glucocorticoids can replace the lack of endogenous glucocorticoids, but also feedback inhibition of hypothalamus-pituitary secretion of excess ACTH to stimulate the excessive secretion of various precursors, and relieve or alleviate masculine symptoms. The patients in this group occurred in genital abnormalities at birth, seriously affecting the patient's physical and mental health, which needed joint treatment of internal and external surgery. The goal of the treatment for adult patients is to improve the quality of life, promote fertility, prevent and treat long-term complications caused by glucocorticoid. Hydrocortisone tablets or long-acting glucocorticoids are preferred for complementary treatment.

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*Correspondence to

Lai Xiaoyang

Endocrine Metabolism Department

The Second Affiliated Hospital of Nanchang University

PR China