Case Report

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The Laparoscopic Oophorocystectomy For A Girl With Primary Amenorrhea And Absence Of Secondary Sexual Development Diagnosed As 17α-Hydroxlyase/17, 20-Lyase Deficiency

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1. Abstract

17α-hydroxlyase/17,20-lyase deficiency(17-OHD) is a rare type of congenital adrenal hyperplasia(CAH), of which only is occupied 1%. The classical symptoms are hypokalemic hypertension caused by overproduction mineralocorticoids and the sexual infantilism caused by suppressed production of sex hormones. This is a case report on a girl phenotypic female admitted in the reproductive endocrinology of the department of Obstetrics & Gynecology Hospital, Fudan university for oophorocystectomy of bilateral cystic ovarian mass, who was found firstly compound heterogenous mutations for p.Y329Kfs and p.A421 of CYP17A1 gene(OMIM 202110). As the patients with 17OHD complain primary amenorrhea and absence of secondary sexual development, it is only diagnosed until puberty. In order to improve the outcomes for 17OHD patients, a timely clinical suspicious, an accurate diagnosis and proper treatments are imperative.

2. Key words:
17α-hydroxlyase/17,20-lyase deficiency, congenital adrenal hyperplasia, primary amenorrhea, absence of secondary sexual developments, ovarian cysts

Abbreviation Congenital adrenal hyperplasia: CAH;
adreno-cortico-tropic-hormone: ACTH;
21-hydroxylase deficiency:21-OHD;
17α-hydroxlyase/17,20-lyase deficiency: 17OHD;
deoxycorticosterone: DOC;
17OH-pregnenolone :17OH-P; in vitro fertilization:IVF.

3. Introduction

Congenital adrenal hyperplasia(CAH) refers to a group of autosomal recessive disorder that causes seven different enzymes deficiency and defect of steroidogenesis process in the adrenal glands. Because of negative feedback on pituitary, impairment of cortisol synthesis stimulates overproduction adreno-cortico-tropic-hormone(ACTH) resulting in the corresponding imbalance of glucocorticoids, mineralocorticoids and/or sex steroids. 21-hydroxylase deficiency(21-OHD) the most common type occupied around 95% CAH cases; while the 11β-hydroxylase deficiency takes possession of the rest 5-8%[1]. Among the other rare types of CAH, approximately 1% cases belongs to 17α-hydroxlyase/17,20-lyase deficiency(17-OHD) with an estimated annual incidence of around 1 in 5000 newborns[2]. Since the rarity and variability of genetic characteristics, the diagnosis and treatment of CAH is still a challenge depending on the type and severity of the enzyme deficiency. P450c17, encoded by gene CYP17A1, involves the activities of both 17α-hydroxlyase and 17,20-lyase to catalyze progenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone respectively. It has been reported that around 120 different mutations of CYP17A1 damage the enzyme activity partially or completely leading to blockage of cortisol synthesis; in return, ACTH accumulates and overstimulates 17-deoxy pathway in zona fasciculataresulting in excessive progesterone, corticosterone and deoxycorticosterone(DOC) [3]. Moreover, the mineralocorticoids hinder rein activity and increase aldosterone effect[2]. Therefore, the

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typical clinical manifestation of 17-OHD is hypokalemic hypertension and absence secondary sexual characteristics with female phenotype; however, not all the clinical features present simultaneously and similarly even in patients bearing the same gene mutation[4]. In this paper, we report a case of a 18-years old girl genetically diagnosed as 17-OHD with hypergonadotropic hypogonadism and experienced a oophorocystectomy by laparoscopy.

4. Case presentation

A 16-years-old phenotypic girl complained of primary amenorrhea and lack of secondary sexual characteristics at the reproductive endocrinology of the department of Obstetrics & Gynecology Hospital, Fudan university on September, 2019. She was 166cm tall and weighted 66.5 kg (BMI 24.13kg/cm2) with normotension. Her karyotype was 46XX. The physical examination showed breast development at Tanner stage V; while the patient had no axillary and less pubic hair at Tanner stage I with normal clitoris. No mass was palpable in the bilateral inguinal areas.The external genitalia were female appearance with atrophic vagina. B-ultrasound revealed infantilism uterus in Table1.

Table 1: The Pelvic ultrasound presentation

uterus size(mm)	**First vist**	**Preoperative**
	25×27×18	30×32×22
Endometrial thick(mm)	2	2
Cervical length(mm)	24	26
Right adnexa(mm)	anechoic area 39×31×16	anechoic area 34×28×35
Left adnexa(mm)	23×15×17(with a few follicles, the biggest 4mm in diameter)	anechoic area 64×43×39

Before our evaluation, she wastaking estradiol/dydrogesterone without menstruation for a month. The biochemical investigation demonstrated a deficit of androgenic sex hormones(dehydroeiandrosterone sulfate, androstenedione) and cortisol; a slightly elevated level of corticosterone and deoxycorticosterone; a raised serum level of 17-hydroxyprogesterone and the normal level of aldosterone(Table2,3). The routine blood examination, liver function, kidney function, and serum electrolyte results werewithin normal. The clinical manifestation and laboratory evaluation were mostly consistent with partial combined 17-OHD, so we analyzed her CYP17 gene.

Table 2: The work-up for primary amenorrhea

		Reference range
LH(mIU/mL)	18.04	Follicular phase: 2.00-12.00
		Luteal phase:1.00-5.00
FSH(mIU/mL)	8.45	Follicular phase:3.30-7.90
		Luteal phase:0.70-5.00
Estradiol(pg/mL)	66	Follicular phase:18.00-195.00
		Luteal phase:50.00-210.00
Progesterone(ng/mL)	2.98	Follicular phase:0.20-1.20
		Luteal phase:5.80-22.10
Free testosterone(pg/mL)	0.2	For female 0.15-0.51
PRL(ng/mL)	11.34	For female 3.50-24.20

FSH, follicle-stimulating hormone; LH, luteinizing hormone;PRL, prolactin.

Table 3: the work-up for CAH

		Reference range
17-OHP(ng/mL)	1.064	Follicular phase:0.10-0.80
		Luteal phase:0.60-2.30
Cortisol(mIU/mL)	10.9	4.82-19.5
DHEA-S(ug/dl)	193.1	19-391.00
Androstenedione(ng/mL)	0.4	0.8-2.8
Corticosterone(ng/mL)	13.594	0.59-12.93
ACTH(pg/mL)	31.3	0-60
Renin activity(ng/ml/hr)	0.595	0.250-0.5820
Aldosterone(pg/ml)	36.3	<280
Na/K/Cl(mmol/L)	142/4.4/104	Na136-145
		K 3.4-5.1
		Cl 98-110

DHEAS, dehydroepiandrosterone sulfate;ACTH, adrenocorticotropic hormone

Genomic DNA were extracted from peripheral blood and applied polymerase chain reaction(PCR) amplification and subclone sequencing to identify the CYP17 gene exons. The result was appeared that two compound heterozygous mutations harbored in the CYP17A1 gene: c.985_987delinsAA, leading to a premature termination codon and amino acid alterations Y329Kfs; and c.1263>A (p.A421) in exon 8, resulting in messenger RNA splicing deficiency and decreased activity of the specific protein enzyme . Oral estradiol valerate(Progynova, 1mg daily) replacement was given to induce secondary sexual development for 6 months. However, the patient was still amenorrhea and had infantile external genitalia. With B ultrasound re-evaluation, it is apparent that the uterus was induce to grow bigger as depicted in Table1; however, the bilateral cystic ovarian mass developed as ultrasound depicted(Table1) and was suspected to be benign tumors. Then she was admitted into hospital for laparoscopic oophorocystectomy. The pathological results indicated that ovarian follicles in various developing phases with a few atretic follicles embedded in the cortex of the bilateral ovarian cysts. The written informed consent was obtained from the patient and her family for the use of her history and examination results in this report.

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5. Discussion

In 1966, Biglieri et al firstly described over 150 cases with details on clinical characteristics, pathophysiology, and genetic mutations of 17-OHD[5]. The initial cholesterol derived from dietary lipids is transported into adrenal cortex where is catalyzed and synthesized into steroid hormone; and, the pathways and enzymology of steroid hormone biosynthesis contain complex mechanisms, deficiency of which can bring about rare disorders of adrenal insufficiency[6]. In the first rate-limiting step, cholesterol is converted to pregnenolone through P450scc coded by CYP11A1 gene on mitochondrial. Subsequently, the microsomal enzyme P450c17 encode by CYP17A1 changes pregnenolone to 17OH-pregnenolone (17OH-P) and DHEA by 17-hydroxylase and 17,20-lyase sequentially in the adrenal zona reticularis. In adrenal zona glomerulosa, microsomal P450c21 converted progesterone to corticosterone by 21-hydroxylated. Therefore, 17-OHD patients characterized with 17-hydroxylase and 17,20-lyase deficiency presents decreased cortisol synthesis in return stimulating ACTH secretion, which promotes mineralocorticoid overproduction. It explains the hypertension and hypokalemia in 17-OHD. Meanwhile, impaired P450c17 enzyme impedes the production of sex hormone production, which clarifies the primary amenorrhea and absence of secondary sexual development in phenotypic females. However, this patient only manifests primary amenorrhea and partial infantilism of secondary sexual development without the characteristics of mineralocorticoid overproduction. That is to say, mutation on CYP17A1 gene can cause complete or partial, combined or isolated 17-OHD[7]. Moreover, 17-OHD patients rarely show adrenal crisis because of the overproduction of corticosterone; therefore, they are usually diagnosed after puberty[8]. For the phenotypic female, they are more likely to visit the gynecologists firstly, and the awareness of the identification these patients is significant for early diagnosis and treatment. According to steroid biosynthesis pathway, it is should be suspected 17OHD when a patient complains of primary amenorrhea and/or absence of secondary sexual development with biochemical evaluation showing hypergonadotropic hypogonadism. It also typically showed in the laboratory results of this patient. It is appropriate to restore hypothalamus-pituitary-adrenal axis and prevent hypogonadism for 17-OHD treatment.

The glucocorticoid treatment aims to reduce ACTH and 11-deoxycorticosterone by physiological 0.25-1.0mg/day dexamethasone and 2-5mg/day prednisone, which could normalize the blood pressure and electrolyte level. Meanwhile, exogenous sex hormone supplement required in 46XX patients in puberty and administered for stimulation and maintenance of secondary sexual development, whereases androgen supplement should be prescribed and genital reconstruction surgery may be performed in 46XY patients who decide to be considered as male. In this case, the patient has been taking estradiol valerate for 6 month to stimulate female characteristics as showed in uterus size; however, the adnexal cysts grows possibly due to hypergonadotropic hypogonadism state. Insufficient steroid sex hormone in incomplete type 17-OHD is not competent to support folliculogenesis, maturation and feedback on FSH/LH secretion which explains the pathological results. In the view of genes, there are more than 100 different CYP17A1 mutations have been reported thatdisplays a distinct ethno-geographic distribution, particularly prevalent in Brazilian[8,9,10]. Genes missense, nonsense mutations, insertions, deletions and splice-site variants all have been identified. The patient in this report was confirmed to bear a compound heterozygous mutation in 17α-hydroxlyase/17,20-lyase activity. It has been initially reported the c.985_987(Y329Kfs) mutation in a 32-year-old Korean phenotypic female in 2003[11], and c.1263 mutation combined with c.985_987(487–489 del) was detected in a 2.5-year-old Chinese phenotypic male in 2011[12]. The functional region of the CYP17A1 gene consists of 10 amino acids binding to the redox partner and P450 oxidoreductase[13], where the impair of this region results in deprivation of hydroxylation then leads to 17-OHD.

The irreversible defect of steroidogensis in 17-OHD interferes the folliculogensis and spermatogensis, rendering the bears of infertility. The reports and study on the fertility treatment of phenotypic female with 17-OHD are still rare. Even though successful follicuar development and oocytes harvest were already reported, only one case reported a donated embryo implants continuing as a viable pregnancy successfully [14]. However, Paulo et al. achieved a successful live birth in a women with partial 17-OHD through in vitro fertilization(IVF) , and the embryo was from the patient herself after meticulous and adequate hormonal control and endometrial preparation[15]. This report may shed light on the fertility treatment of patients with 17-OHD.

6. Conclusion

In conclusion, the diagnosis of 17-OHD is difficult because of its rarity and variety on clinical symptoms. Although the mechanism of adrenal steroidogensis and mineralocorticoids is now well understood and clarified, the associated genes mutations are still unveiled. In this case, the patient is a compound heterozygous mutation of p.Y329Kfs and p.A421 which is first reported in the same patient. To improve the outcomes for the patients, a timely clinical suspicious, an accurate diagnosis and proper treatments are imperative.

7. Declarations

Ethics approval and consent to participate

The paper was approved by ethics committee at Obstetrics and Gynecology Hospital, Fudan University.

Consent for publication

Written informed consent was obtained from the patient's mother for publication of this case report.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Author contributions

XX and WZ contributed to the conception of the paperand helped perform the analysis with constructive discussion. LW and XC contributed significantly to analysis and manuscript pre-paration. LWperformed the data analyses and wrote the report. PZ gave the critical revisions.

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