A 9-Year-Old Girl Presenting Central Precocious Puberty with Polycystic Ovary Syndrome

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Abstract. A 9-year-old girl presented central precocious puberty (CPP) with polycystic ovary syndrome (PCOS) simultaneously. She had obesity, hirsutism and acanthosis nigricans. Laboratory examination revealed high levels of serum LH, FSH (LH > FSH), testosterone and insulin. The response of dehydroepiandrosterone sulfate after administration of ACTH was normal for a female. She has been treated with GnRH analog and weight reduction. Excessive androgen production results from ovarian defect and therefore, functional ovarian hyperandrogenism and hyperinsulinemia might be major factor in the pathogenesis. This case is the first report of a PCOS woman demonstrating CPP simultaneously.

Key words: central precocious puberty, polycystic ovary syndrome, hyperinsulinemia, hyperandrogenism, GnRH analog

Introduction

Polycystic ovary syndrome (PCOS) was described by Stein and Leventhal in 1935 (1) and characterized by chronic anovulation and hyperandrogenism. Possible causes are dysregulation of LH secretion by the hypothalamus or abnormalities of ovaries or adrenal glands or hyperinsulinemia, but its etiology remains unknown (2-4).

We report the first case of a PCOS patient demonstrating central precocious puberty (CPP) simultaneously. Some reports show patients with CPP followed by PCOS and suggest some

relationships between these diseases, which involve abnormal regulation of gonadotropin secretion (5-10). The mechanism in a PCOS girl presenting CPP remains unknown.

Case Report

A 9-year 7 month-old girl was referred because of vaginal bleeding. She was born uneventfully after a full-term gestation. Birth weight was 3422 g and length was 49.5 cm. She showed signs of obesity from the age of 4 (23.3% above the ideal weight for height). She was first noted to have bilateral breast development at the age of 7, followed by pubic hair growth at the age of 8. Her height velocity was increased and obesity and hirsutism had progressed since seven years of age.

On the first visit to our hospital, her height and weight were 147.7 cm (2.35 SD) and 66.3 kg (body

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Table 1 Laboratory findings at diagnosis

GH	0.8 ng/ml	UA	6.8 mg/dl
IGF-I	837 ng/ml	GOT	19 U/l
TSH	1.45 μ U/ml	GPT	11 U/l
T ₃	206 ng/dl	ALP	1089 U/l
T ₄	8.6 μ g/dl	T-cho	152 mg/dl
LH	6.1 mIU/ml	TG	159 mg/dl
FSH	3.6 mIU/ml	glucose	88 mg/dl
HCG	<1.0 mIU/ml	insulin	19 μ U/ml
PRL	17.2 ng/ml	(insulin/glucose=0.22)	
E ₁	49.0 pg/ml	CPR	3.4 ng/ml
E ₂	98 pg/ml	HbA _{1c}	4.8 %
testosterone	100 ng/dl	urinary	
DHEAS	1210 ng/ml	glucose	(-)
17-OHP	3.6 ng/ml	ketone body	(-)

Table 2 Endocrinological data at diagnosis

			0 min	30 min	60 min	90 min	120 min
LH-RH test	LH	(mIU/ml)	6.1	52.8	63.2	75.6	95.7
	FSH	(mIU/ml)	3.6	10.3	13.3	17.6	21.7
	E ₂	(pg/ml)	98				129
TRH test	TSH	(μ U/ml)	1.45	8.64	6.27	4.39	3.65
	PRL	(ng/ml)	17.2	23.5	15.4	12.8	14.7
Arginine tolerance test	GH	(ng/ml)	27.4	28.6	39.9	30.6	18.0
Insulin tolerance test	GH	(ng/ml)	4.1	1.3	6.3	15.3	27.4
	cortisol	(μ g/dl)	10.8	17.6	14.0	18.2	24.9

mass index: 30.4), respectively. The breast and pubic hair were at Tanner stage IV and III, respectively. She had hirsutism and acanthosis nigricans. Her bone age assessed by the Greulich-Pyle method was 12 yrs old.

Laboratory examination revealed high levels of serum LH, FSH (LH > FSH) and testosterone (Table 1). The basal and maximal concentrations of LH after administration of LH-releasing hormone (LHRH) were high, although the levels of FSH remained in the normal range (Table 2). The basal concentration of TSH was normal and the peak level after TRH administration was also normal (Table 2). Although the basal concentration of PRL was slightly increased, the peak level after TRH administration was normal

(Table 2). The ratio of serum insulin to plasma glucose was slightly elevated ($19/88 = 0.22$) (Table 1). Ultrasonography and magnetic resonance imaging (MRI) of the abdomen revealed bilateral polycystic ovaries (Fig. 1A, B). MRI of the pituitary gland showed no central nervous system abnormalities including hypothalamic-pituitary tumors (Fig. 2A, B). After eight months' treatment with GnRH analog, the basal levels and maximal responsiveness of dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone and 17 α -hydroxyprogesterone (17-OHP) in response to administration of ACTH were normal for pubertal females (Table 4). On the basis of these investigations, PCOS with CPP was diagnosed.

She has been treated with GnRH analog and

Fig. 1 Unenhanced sonogram (A) and axial unenhanced T2-weighted MR image (B) of ovary at diagnosis.

Fig. 2 Sagittal (A) and coronal (B) unenhanced T1-weighted MR image of pituitary gland at diagnosis.

Table 3 Serum hormone concentrations after 4 months of GnRH analog treatment

IGF-I 707 ng/ml,	DHEAS 1170 ng/ml				
Fasting plasma glucose,	79 mg/dl, insulin 13 μ U/ml				
Postprandial plasma glucose,	94 mg/dl, insulin 30 μ U/ml				
LH-RH test					
	before	30 min	60 min	90 min	120 min
LH (mIU/ml)	0.6	1.7	1.2	0.9	0.8
FSH (mIU/ml)	3.3	4.9	4.3	4.2	4.1
E ₂ (pg/ml)	<10				<10
testosterone (ng/dl)	30				30

Table 4 Responses to rapid ACTH test after 8 months of GnRH analog treatment

		0 min	30 min	60 min
cortisol	(μ g/dl)	23.8	25.7	31.8
progesterone	(ng/ml)	1.1	1.5	1.5
17-OHP	(ng/ml)	3.0	3.7	3.6
androstenedione	(ng/ml)	2.3	2.4	2.3
DHEAS	(ng/ml)	2120	1850	1690
testosterone	(ng/dl)	20	30	20

weight reduction induced by a standardized hypocaloric diet consisting of 1500 kcal daily based on the food exchange list of the Japan Diabetes Society and an exercise program. Treatment with GnRH analog resulted in prompt cessation of breast development and vaginal bleeding and arrested progression of hirsutism along with a deceleration of growth velocity and bone maturation. Adequate suppression was biologically documented by reductions in the concentrations of basal LH, estradiol, PRL, and testosterone and prepubertal response to LHRH testing (Fig. 3, Table 3). Likewise, the ratios of LH to FSH at baseline were normalized after treatment. The DHEAS levels were within the normal range and did not change after GnRH analog treatment. Basal serum insulin levels were decreased after dietary weight reduction. As noted in Fig. 4, the MR image after 4 months of GnRH analog treatment showed

regression of polycystic ovaries.

Discussion

The endocrinological features of PCOS are hyperandrogenism, increased concentration of LH or an increase in the ratio of LH to FSH, and increased levels of estrone and insulin. The pathogenesis of PCOS has been variously ascribed to primary abnormalities of LH regulation, ovaries, adrenal glands or recently hyperinsulinemia. But the etiology of this disorder including the source of androgen remains elusive.

If a girl develops secondary sexual characteristics before the age of seven years, she is considered to have sexual precocity. Our patient was diagnosed as CPP on the basis of the early onset of thelarche, pubarche, menarche, increased height velocity and advanced bone maturation.

Vaginal bleeding				admission for weight reduction						
Leuporelin		1.88mg			3.75mg
	before	1month	2months	3months	4months	5months		8months		
basal LH	6.1	9.1	2.8	0.8	0.6	0.5		0.4		
basal FSH	3.6	6.4	3.9	3.0	3.3	1.8		2.8		
E ₂	98	<10	<10	<10	<10	<10		<10		
PRL	17.2		7.6	7.0		6.4		12.7		
testosterone	100	60	50	40	30	30		20		
DHEAS	1210	980	1330	1070	1170			1230		
IGF-I	837	878	817	681	707	684		741		
ALP	1089	1039	1021	854	764	715		759		
fasting insulin	19	128	25	153	30	8		18		
fasting glucose	100	95	84		94	80		86		
BW	66.3	67.0	66.0	67.7	62.5	60.9		66.0

Fig. 5 Mechanism of ovarian steroidogenesis.

production per cell were more noticeably increased in propagated theca cell cultures from PCOS than in controls (11, 12). *17 α -hydroxylase/17,20-desmolase* (CYP17), *3 β -hydroxysteroid dehydrogenase* (*3 β -HSD*), steroidogenic acute regulatory protein (*StAR*) and cholesterol side chain cleavage enzyme (CYP11A) activities per theca cell are augmented in PCOS theca cells compared with normal cells, and therefore it is proposed that excess androgen production in PCOS results from dysregulation of CYP17 enzyme, the key enzyme required for androgen production in theca cells, activity due to an intrinsic ovarian defect. LH first stimulates P450c17 gene expression. As LH stimulation continues, reduction of P450c17 messenger ribonucleic acid (mRNA) and enzyme content ensues in theca cells. The total *5 α -reductase* activity was approximately 4-fold higher in PCOS follicles than in control follicles and the high concentrations of 5-reduced androgens, *5 α -*

androstane-3,17-dione produced from androstenedione, in polycystic ovaries are capable of greatly inhibiting human granulosa cell aromatase activities by functioning as a competitive inhibitor and suppress estradiol production by 75% (13, 14). Yong *et al.* reported that treatment with FSH, but not LH, increased aromatase activity in immature granulosa cells (15).

Recent data also suggest in that steroidogenic enzyme mRNA may be overexpressed in PCOS theca cells, and the mean levels of LH receptor mRNA expression were higher in theca cells and granulosa cells from polycystic ovaries than in control follicles (16). Granulosa cells from women with polycystic ovaries prematurely respond to LH (17). If LH levels are raised above a certain threshold level, premature luteinization may be started. The theca cells are hyperstimulated and granulosa cells may be prematurely luteinized. Premature exposure of granulosa cells to LH

inhibits their proliferation. A balance between FSH and LH is required for follicle development and ovulation, such that development of the dominant follicle is arrested. This may be important in the mechanism of anovulation in PCOS.

Although our patient has a high concentration of LH and imbalance between FSH and LH, she has shown signs of premature menarche and the mechanism remains unknown. In this case, gonadal suppression therapy resulted in reduction in the concentrations of LH, FSH, estradiol and testosterone; otherwise the DHEAS level was within the normal range: decrease in the high level of LH followed the decrease in the testosterone concentration. The rapid ACTH stimulation produced normal responses of serum 17-OHP, DHEAS, androstenedione and testosterone after gonadal suppression therapy. It is speculated that the hyperandrogenism in this case might be caused by hypothalamic-pituitary dysfunction of gonadotropin secretion and ovarian androgens, but not by the adrenal gland.

The ovarian androgen excess is usually accompanied by hyperinsulinemia and dyslipidemia in PCOS (2, 3). PCOS is associated with an increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus resulting from profound reductions in insulin sensitivity and insulin secretory dysfunction, and inheritability of β -cell dysfunction is likely to be a significant factor in the predisposition to diabetes (18). Adashi *et al.* (19) reported that *in vitro* treatment of primary culture cells from rat anterior pituitary incubated for two days in the presence of insulin resulted in significant increases in both the basal and the maximal release of LH and FSH. Therefore, gonadotroph constituted a target cell of insulin, and insulin might act directly on the anterior pituitary in the regulation of gonadotropin release. An increased insulin level in PCOS may be a major factor causing premature maturation of granulosa cells and increase the ability of granulosa cells to respond to LH. Hyperinsulinemia may play a pathogenetic part in

hyperandrogenism in women with PCOS by increasing ovarian CYP17 enzyme activity and decreasing the serum sex hormone binding globulin (SHBG) concentration (3). Nestler *et al.* reported that insulin and IGF-I stimulated human thecal testosterone biosynthesis with inositolglycans as the signal transduction system in the PCOS (20). Dietary weight reduction and exercise have been shown to decrease ovarian P450c17 α activity and serum free testosterone concentrations and improve insulin sensitivity, LH levels, menstrual disturbance and infertility in obese women with PCOS (21–23). Insulin-sensitizing treatment, with such as metformin and troglitazone, has been reported to ameliorate hyperinsulinemia, hirsutism, hyperandrogenism, and to restore ovulation in women, reducing ovarian cytochrome P450c17 α activity (24–26). Although our patient still showed signs of obesity and hyperinsulinemia before weight reduction therapy, her testosterone concentration was decreased with gonadal suppression therapy. Dietary weight reduction and exercise might contribute to improvement of hyperinsulinemia. Therefore, the role of obesity and hyperinsulinemia in development of the gonadotropin-ovary system and hyper-androgenism might be small in this case.

Frankly masculinizing plasma concentrations of androgens are capable of inducing the histological changes in PCOS in the ovary and bringing about follicle maturation arrest (4). In virilizing classic CAH, polycystic ovaries may be caused by the same mechanism. Excessive production of adrenal androgens can supply substrate for extragonadal aromatization and result in tonic estrogen inhibition of FSH secretion. Although CPP may occur when the prepubertal child has previously been exposed to excessive levels of endogenous or exogenous androgens, most patients with premature adrenarche enter puberty and experience menarche within the normal age range. On the other hand, hyperinsulinemia can stimulate adrenal and

ovarian steroidogenesis. Insulin resistance accompanies puberty and may contribute to adrenarche (3). In our case, the DHEAS level was within the normal range in the clinical course and the rapid ACTH stimulation produced normal responses of serum DHEAS, androstenedione and testosterone after gonadal suppression therapy. Therefore her hyperandrogenism might not result from excessive production of adrenal androgens.

The mechanism of a PCOS girl presenting CPP remains unknown. Hyperinsulinemia, increased early insulin responses to glucose, increased glucose uptake rate in peripheral tissues, high free androgen indexes, and decreased SHBG and IGF binding protein-1 levels are present in most girls with CPP, which is closely related to the characteristics of PCOS (27).

Some pathways including steroid hormone synthesis, gonadotropin action and the insulin signaling mechanism have been implicated in the etiology of PCOS. To understand the complex genetics of PCOS, several genes from these pathways have been tested as candidate genes. CYP11a, encoding P450 cholesterol side chain cleavage, the insulin gene (INS) variable number tandem repeat (VNTR), and follistatin gene appear to be potential disease loci for PCOS (28). Although abnormalities in the regulation of 17 α hydroxylase/17,20 lyase in PCOS have been reported, linkage analysis excluded CYP17 as a major susceptibility gene for PCOS. The INS-VNTR has been shown to be involved in the regulation of insulin gene expression and implicated in the etiology of type 2 diabetes. Follistatin, an activin-binding protein, neutralizes the biological activity of activin and may function as a reservoir for activins (29). Activin promotes ovarian follicular development, inhibits theca cell androgen production, and increases pituitary FSH secretion. Overexpression of follistatin in transgenic mice results in the suppression of serum levels of FSH and arrested ovarian folliculogenesis (30). These are all characteristic features of PCOS.

In conclusion, in this patient with PCOS

presenting CPP, which is the first report, excess androgen production results from an ovarian defect. Functional ovarian hyperandrogenism and hyperinsulinemia might play a major pathogenetic part, but details of the mechanism remain unknown.

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