HIRSUTISM IN ADOLESCENTS: HORMONAL PATTERN AND OVARIAN MORPHOLOGY*

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SUMMARY

We have made endocrinologic, symptomatologic and utrasonographic studies in 38 adolescent (≤18 years of age) patients with the complaint of hirsutism. 15 age-matched subjects were taken as control. The following results were obtained: 1-The causes of hirsutismus in the study group were polycystic ovarian syndrome (PCOS) (57.9%) (n=22), idiopathic hirsutism (IH) (39.5%) (n=15) and late-onset adrenal hyperplasia (LOHD) (2.6%) (n=1). 2- Total testosterone (tT), free testosterone (fT), androstenedione (A) and dehidroepiandrostenedione (DHEAS) levels were significantly higher in hirsute patients than the controls. 3- There was no statistically significant difference in terms of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), thyroid stimulating hormone (TSH) and 17-hydroxy-progesterone (17-OHP) with the study group and the controls. 4-Menstrual irregularities were significantly higher in PCOS group than in the IH group. 5-In PCOS girls the mean ovarian volume and serum estradiol (E_2) levels were significantly higher than IH group and controls. From the above findings, we suggest that clinical examination, endocrinologic and ultrasonographic investigation must be required in the evaluation of hirsute adolescent girls as considering the heterogenity of the etiology.

Key Words: hirsutism; adolescence; polycystic ovary syndrome; idiopathic hirsutism; late-onset adrenal hyperplasia

INTRODUCTION

Hirsutism has been defined as excessive hair growth in anatomical sites where such growth may be considered a secondary male characteristics and is a sensitive marker for increased androgen action.

The pilosebaceous unit of sexual hair is androgen responsive to dihydrotestosterone (DHT), the primary nuclear androgen in steroid-sensitive hair follicles. The degree of stimulation of terminal hair and therefore the development of hirsutism is a reflection of the combined effects of the local levels of androgens available as a precursor, the status of the androgen receptor and the ability to form DHT by 5-alpha-reductase activity.

Clinical evaluation of hirsutism represents an evaluation of the causes of hyperandrogenism. Although the most common causes of hirsutism are 'idiopathic' and secondary to chronic anovulation with polycystic ovary syndrome (PCOS), an increase in the production of androgens from the adrenal gland and ovary must be evaluated to exclude some diseases such as Cushing's syndrome, congenital adrenal hyperplasia and adrenal or ovarian tumors.

PCOS is a clinical disorder associated with menstrual irregularity, hirsutism, and obesity. It is characterized by disordered gonadotropin secretion, acyclic estrogen production and hyperandrogenism (1,2), which is usually perimenarcheal in onset (3). Several cases of PCOS have been diagnosed within the perimenarcheal period (4,5). When systematically evaluated in adolescents, its prevalence is surprisingly high, not only in patients with menstrual disorders, acne or obesity but also in some patients who show no symptoms or signs of hyperandrogenemia (6,7).

In this study we studied the clinical, sonographic and hormonal aspects of hirsutism in adolescents in order to clarify this well-known but little evaluated subject in adolescents. The aim of our study was to investigate the possible causes of hirsutism in adolescent girls and once the diagnosis was established to compare the clinical, sonographic and hormonal data in order to emphasize the importance of these parameters in the diagnosis of hirsutism. Thirty-eight hirsute adolescents were evaluated and compared with 15 age-matched normal girls.

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MATERIALS AND METHODS

Thirty-eight unselected adolescent subjects, whose ages ranged from 14 to 18 years, with a mean age of 17 years, who presented with hirsutism with or without menstrual dysfunction to our Gynecologic Endocrinology outpatient clinic between the period of April to August 1992 were studied.

Hirsutism was defined according to the criteria of Ferriman and Gallway (8), who graded nine hormone-sensitive body areas from 0 to 4. Scores of less than 8 were considered nonhirsute; 8 to 16, mild hirsutism and 17 to 25, moderate hirsutism.

The ovarian morphology was assessed by transvaginal ultrasonography. The ovary was defined as polycystic if there were multiple cysts (10 or more) 2-8 mm in diameter arranged either peripherally around a dense core of stroma or scattered through an increased amount of stroma or both (9).

Twenty-two patients were clinically diagnosed as having PCOS on the following criteria: (1) normal regular cycles or oligoamenorrhea associated with the presenting hirsutism with or without clinical enlargement of the ovaries; and/or (2) an increased serum luteinizing hormone (LH)/ follicle stimulating hormone (FSH) ratio; and (3) confirmatory ultrasonographic evidence of the ovary defined as polycystic according to the criteria of Adams et al (9). Fifteen patients presenting with hirsutism without PCOS and no evindence of an ovarian or adrenal neoplasm, prolactinoma or Cushing's syndrome were termed as idiopathic hirsutism (IH). One patient was diagnosed as having late-onset adrenal hyperplasia (LOHD). The normal follicular phase plasma 17-hydroxyprogesterone (17-OHP) in our laboratory is < 1.8 ng/ml. This patient presented with hirsutism and amenorrhea and had ultrasonographic evidence of polycystic ovary (PCO) and she had a basal 17-OHP value of 5.2 ng/ml. This patient was then injected with 0.25 mg synthetic adrenocorticotropic hormone (ACTH) (Synacthen Depot Ampul 0.5 mg, Ciba, Turkey). Additional plasma level of 17-OHP obtained 60 minutes after the intravenous administration was 6.5 ng/ml. A plasma 17-OHP response greater than the upper range of the normal general population indicates a 21-hydroxylase (21-OH) deficiency, according to the data of New et al (10).

None of the patients had taken any medication during the past 3 months and had hyperprolactinemia or clinical evidence of hypercortisolism or thyroid dysfunction. A careful family history was obtained from all subjects in the study. Informed consent was obtained from all patients. The age matched control group comprised 15 volunteers with normal ovaries on ultrasound and regular ovulatory cycles.

The pubertal development stage for breast and pubic hair was recorded according to the Tanner's classification (11).

Morning samples of plasma total testosterone (tT), free testosterone (fT), androstenedione (A), dehydroandrosterone sulfate (DHEAS), 17-OHP, thyroid stimulating hormone (TSH), FSH, LH, estrodiol (E2), and prolactin (PRL) were performed in the early follicular phase (day 2-4) or at random in amenorrheic ones.

The menstrual history was defined as amenorrhea, oligomenorrhea, regular (lasting at least 21 days or at most 35 days, with no more than a 4-day variation in lenght between cycles in individual subjects) or irregular (cycle lenght between 21-35 days but more than a 4-day variation).

All ultrasonographic examinations were performed by the same experienced physician with a Combison 320-S Kretz Technik (5 Mhz convex probe). The ovarian volume was calculated as $^1/_2 \times d_1 \times d_2 \times d_3$ (d_1 = maximal transverse diameter, d_2=maximal longitudinal diameter, d_3 = maximal anteroposterior diameter) in the absence of a dominant follicle.

The body mass index (BMI) represented the ratio of body weight (kg) and the square of the height (m).

Radioimmunoassays (RIA) for LH, FSH, E_2, tT, fT, A, DHEAS, PRL, 17OHP were performed by standard techniques in our laboratory (Immuno Diagnostic Systems Limited, England; Diagnostic Products Corporation, USA; Diagnostic Systems Laboratories Inc., USA).

For comparison of variables of hirsutic group and controls unpaired Student's t-test was used. For comparison of serum hormone levels, ovarian volume, BMI and age of the group of PCOS patients, IH patients and the controls, one way ANOVA followed by an unpaired Student's t-test was used. To test the significance of differences in menstrual cycle pattern between PCOS group and IH patient group chi-square and Fisher's exact tests were used. A $p < .05$ was regarded as significant. Values are shown as mean ± SE.

RESULTS

Out of 38 hirsute adolescent patients presenting to our Gynecologic Endocrinology outpatient clinic, 22 patients (57.9%) were diagnosed as having PCOS, 15 patients (39.5%) were dignosed as having IH and one patient (2.6%) with abnormal elevation of 17-OHP after ACTH stimulation test was considered heterozygote for 21-hydroxylase deficiency.

There were no statistically significant differences between the hirsutic and regularly menstruating control girls with respect to the mean age, age at menarche, gynecologic age, and BMI (Table I). Pubertal development of the two groups was similar. All girls had reached stage 4 or 5 of the breast and pubic hair development.

Table I: Mean Age, Age at Menarche, Gynecologic Age, Ovarian Volume and BMI in Adolescent Hirsutic and Regularly Menstruating Control Girls*.

	Hirsutic group (n=38)	Control group (n=15)
Age (yrs)	17.4 ± 0.2	16.9 ± 0.4
Age at menarche	12.9 ± 1.2	13 ± 1.3
Gynecologic age (yrs)	4.3 ± 1.1	4.1 ± 1.3
BMI (kg/m^2)	22.8 ± 1.4	23.7 ± 1.5
Ovarian volume (cm^3)	8.8 ± 1.2	6.1 ± 0.9

*: no significance between groups.

Table II: Comparison of variables between PCOS patients, idiopathic hirsute patients and the controls.

Variable	PCOS group (n=22)	Idiopathic Hirsute group (n=15)	Control Group (n=15)
Age (yrs)	17.4 ± 0.3	17.3 ± 0.2	16.9 ± 0.4
BMI (kg/m^2)	22.5 ± 1.3	23.1 ± 1.4	23.7 ± 1.5
LH (IU/L)	17.4 ± 4.1	12.8 ± 3.1	9.1 ± 1.1
FSH (IU/L)	6.9 ± 0.5	8.6 ± 2.5	7.1 ± 1.2
E2 (pg/ml)	57.5 ± 9.3*!	25.3 ± 10.3	31.1 ± 7.6
PRL (ng/ml)	8.7 ± 2.1	6.8 ± 1.5	5.7 ± 1.4
tT (ng/dl)	114.6 ± 13.2**!!	98.8 ± 16.1**!!	56.8 ± 6.7
fT (ng/ml)	2.79 ± 0.5*!!	3.8 ± 0.7*!!	1.4 ± 0.3
A (ng/ml)	2.72 ± 0.3**!!	3.3 ± 0.4**!!	1.5 ± 0.3
DHEAS (ug/dl)	326.1 ± 31.2*!!	362.1 ± 41.3*!!	215.2 ± 35.4
TSH (IU/L)	2.05 ± 0.3	1.88 ± 0.6	1.75 ± 0.4
17-OHP (ng/ml)	1.33 ± 0.2	1.65 ± 0.3	1.33 ± 0.4
Ovarian volume (cm^3)	9.9 ± 1.1*!	7.3 ± 1.1	6.1 ± 0.9

*: $p < 0.05$, **: $p < 0.01$; ! PCOS vs. Idiopathic Hirsute and Control group; !!PCOS and Idiopathic Hirsute group vs. Control group.

Table III: Menstrual Pattern of PCOS and Idiopathic Hirsutic Group

	PCOS group (n=22)	Idiopathic Hirsutic group (n=15)
Normal Regular Cycles	2/22 (9.1%)*	11/15 (73.3%)
Irregular Cycles	5/22 (22.7%)	2/15 (13.3%)
Oligomenorrhea	11/22 (50%)**	1/15 (6.6%)
Amenorrhea	4/22 (18.2%)	1/15 (6.6%)

*: $p < 0.001$, **: $p < 0.05$

Mean plasma levels of tT ($p < 0.01$), fT ($p < 0.05$), A($p<0.01$) and DHEAS ($p<0.05$) were significantly higher in PCOS group and in IH group than the controls, while there was no statistically significant difference in terms of gonadotropins, PRL, TSH and 17-OHP (Table II).

Mean plasma E2 values and the mean ovarian volumes of PCOS group were significantly higher than those of the IH group and the control group ($p < 0.05$).

Menstrual irregularities were observed more often in the PCOS girls than the IH girls. Normal regular cycles were observed in 11 of the 15 IH girls (73.3%) and in 2 of the 22 PCOS girls (9.1%). The difference was significant ($p < 0.001$). Oligomenorrhea was evident in 11 of the PCOS girls (50%) and in 1 of the IH girls (6.6%). The difference was significant too ($p < 0.05$) (Table III).

Thirty - eight patients with hirsutism showed mild to moderate hirsutism. None of them showed evidence of virilization, such as clitoral hypertrophy, deepening of the voice or increase in muscular development.

In the IH group out of 15 patients, 11 (73.3%) had mild and 4 (26.6%) had moderate hirsutism. In the mildly hirsute group plasma androgens were normal in 7 subjects, while in the moderately hirsute group at least one plasma androgen was elevated.

In the PCOS group out of 22 patients, 20 (91%) had mild hirsutism, 2 (9%) had moderate hirsutism. 10 of the mildly hirsute PCOS patients had normal plasma androgen levels. In two moderately hirsute PCOS patients plasma androgens were elevated.

DISCUSSION

In our study population 57.9% of the adolescent hirsutic girls were diagnosed as having PCOS, 39.5% as having IH and 2.6% LOHD. Our results showed that these hirsutic adolescent girls had significantly higher plasma concentrations of tT, fT, A, and DHEAS than regularly menstruating control girls.

In hyperandrogenic patients it is not always clear whether the excess androgen arises from adrenal or ovarian sources. Approaches to assessment of ovarian and adrenal contributions to circulating androgens have included selective adrenal and/or ovarian suppresion and stimulation tests as well as measurement of androgens in the adrenal and ovarian veins (12,13). A selective catheterization of both adrenal and ovarian blood vessels in hyperandrogenized patients demonstrates that purely ovarian or adrenal androgen production is not very frequent (<39%) (14,15).

The ovarian androgens (T and A) have shown to be increased in adolescent hirsute patients in this study, but also the mean plasma DHEAS, which is primarily adrenal origin was higher in hirsute girls and several of our patients had high levels of DHEAS above the normal limits of our laboratory. These findings show that elevated adrenal androgen production is fairly common as well as ovarian androgen production in hirsute adolescent girls. Several authors have reported an important adrenal contribution to androgen production in PCOS (12,14)

Although the mean plasma androgens were higher in hirsute adolescent girls than the controls, in 7 patients of the mildly hirsue IH girls and in 10 patients of the mildly hirsute PCOS girls the plasma androgens were not elevated. Possible mechanisms are: 1-SHBG levels may be decreased in hirsute patients, allowing a higher fraction of bioactive androgens in spite of normal total serum androgen levels. 2- (a) - The activity of 5-alpha-reductase in the skin of hirsute patients may be different from that of similar nonhirsute females. Both direct measurements of the enzyme from skin cultures (16) and measurements of 3 androsteno - diol glucuronide (a metabolite of DHT) (17) have a direct correlation with the degree of hirsutism. (b) - Hirsute women may convert T to DHT at rates similar to normal males; normal women should have one fourth of that rate (18). 3- Increased receptor sensivitiy to androgens.

It has previously been reported that patients presenting with PCOS and/or IH may indeed be patients with the LOHD, which may only be detected by means of ACTH stimulation (19). A hyperresponse of plasma 17-OHP, 60 minutes after intravenous ACTH injection, strongly suggests the diagnosis of 21-OH deficiency. However, two investigators (20,21), claimed that this test is not cost-effective in the evaluation of hirsute patients and that it must be restricted to patients who are suspected of having LOHD on the basis of clinic criteria. In this study ACTH stimulation test was only performed in one patient whose basal 17-OHP level was above the normal value.

Our results showed that the frequency of normal regular cycles was significantly lower and oligomenorrhea was significantly higher in PCOS girls than the IH girls. It is demonstated that anovulatory cycles of adolescent girls are associated with increased serum concentrations of LH, T, and A (22).

In this study by ultrasography, the mean ovarian volume of PCOS girls was found to be higher than the IH girls and the controls. Venturoli et al (23) evaluated adolescents with menstrual irregularities by ultrasography and reported 57.9% multicystic ovaries in subjects with irregular menses and these had higher ovarian volumes than adolescents with regular menses. Pelvic ultrasography has provided us with a precise and noninvasive method of assessing the presentation and prevelance of polycystic ovaries in adolescent girls with hirsutism.

In conclusion, on the basis of these results, we suggest that hirsutic adolescent girls to be evaluated clinically, endocrinologically and ultrasonographically

regarding the heterogeneity of the etiology. Further examinations should be performed in patients who are suspected of having ovarian or adrenal hyperandrogenic states such as late-onset adrenal enzyme defects on the basis of clinical and hormonal study.

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