Etiologic Factors and Clinical Characteristics of Turkish Adolescent Girls Diagnosed with Hirsutism

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Hirsutism In Turkish Adolescent Girls

Özet

Anahtar Kelimeler
Türk; adolesan; kız; hirsutizm

Abstract
Aim: Hirsutism is the male type terminal hair growth in androgen sensitive body areas of the female gender. There is a limited number of studies that involves only hirsutic adolescents. In this study, clinical and laboratory characteristics of hirsutism in Turkish adolescents were evaluated. Material and Method: 174 hirsutic adolescent girls were assessed for menarche age, menstruation cycle, family history, body mass index z-scores, modified Ferriman-Gallwey (mFG) scores, hair development and distributions and laboratory findings. Results: Mean age was 15.4±1.5 years. The cases were identified as polycystic ovary syndrome (PCOS), 57.4% idiopathic hirsutism (IH) 29.3% and adrenal hirsutism (AH) 13.2%. The mean ages, hair development onset and menarche ages of the groups were similar. Mild, moderate and severe hirsutism were determined in 132, 39 and 3 cases respectively. Maximum hair development was observed at the thigh, upper arm and lower back areas; minimum hair development was observed in the upper abdomen, upper back and chest areas. The menstrual irregularity, obesity and LH/FSH ratio were significantly higher while SHBG was significantly lower in the PCOS. Discussion: PCOS is the most frequent reason for adolescent hirsutism with menstrual irregularity, mild hair growth and obesity. Regular menstruation suggests firstly idiopathic hirsutism, mFG score values of the thigh, upper arm and lower back areas may provide a preunderstanding for hirsutism. Upper lip area’s where frequent epilation is applied may be deceptive concerning scoring.

Keywords
Turkish; Adolescent; Girl; Hirsutism
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Introduction
Hirsutism is the terminal hair growth in androgen-sensitive body areas of the female gender. Its prevalence varies between 5-15% depending on the ethnic and racial origin [1]. The percentage is higher among Middle Eastern societies. It is reported as 18-32% for Turkey [2,3]. The main causes of hirsutism are polycystic ovary syndrome (PCOS), idiopathic hirsutism and adrenal hyperplasia. The differential diagnosis includes hyperprolactinemia, Cushing syndrome and virilizing tumors [1].

Polycystic ovary syndrome is the most common cause of hirsutism that affects 1.1-9.1% adolescent girls. PCOS cases present symptoms of menstrual irregularity, hirsutism, acne and obesity [4-5]. Diagnosis criteria for adolescent patients are menstrual irregularity (oligomenorrhea at least 2 years have passed after menarche), hyperandrogenism; clinical (hirsutism, acne and alopecia) or biochemical (elevated blood androgens), polycystic ovaries with increased volume (>10 ml) [6].

Non-classical congenital adrenal hyperplasia (NCAH) prevalence was reported 0.6% to 9% in women with androgen excess that causes the clinical features. The most symptoms among adolescent girls are hirsutism (59%), menstrual dysfunction (54%) and acne. 21-hydroxylase deficiency is a common autosomal recessive disorder of adrenal steroid synthesis. Other steroidogenic enzyme deficiencies such as 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase are rare in hirsutism [7].

Idiopathic hirsutism (IH), defined as normal ovulation with normal adrenal function and androgen levels, is a relatively common cause of hirsutism. It is seen 5-15% of hirsutic cases. IH may be associated with androgen receptor gene polymorphisms. Aromatase and 5-alpha reductase enzyme activity disorders have been postulated to explain the pathogenesis of IH [8].

After the initial hirsutism scoring systems, nowadays modified Ferriman-Gallwey (mFG) is preferred for the quantification of body hair. A total score of >8 is accepted as hirsutism [2,9]. In Turkey, most studies analyzed adult and adolescent hirsutism cases together so far. However, there is a limited number of studies on hirsutism that involves only the adolescents. In this study, we aimed to assess the mFG scoring system, to reflect the clinical and laboratory characteristics of hirsutism at the Turkish adolescent females.

Material and Method
174 adolescent female cases, who have referred to Antalya Training and Research Hospital, Pediatric Endocrinology Department with the complaint of body hair growth between June 2012-September 2015 and diagnosed with hirsutism, were investigated. The cases were questioned with regards to menarche age, menstruation cycle, the onset of hair development, family history of hirsutism, drug use and other diseases. Their body weight and sexual hair growth were evaluated. The menstrual cycle that is 21-45 days long for first two years and 21-35 days long afterwards was designed as regular while other durations were accepted irregular. Primary amenorrhea is defined as the absence of menstruation in a woman by the age of 16 while secondary amenorrhea is the cessation of an established menstruation for six months in a woman of reproductive age [10].

The body mass index (BMI) was calculated by dividing the body weight (in kilograms) by the height (in meters) squared (weight/height2). According to BMI standard deviation scores (BMI SDS) of the cases, those lower than -2 SD were regarded as low weight, those between -2/+1 SD as normal weight, those higher than +1 SD as overweight and those higher than +2 SD as obese [11].

mFG was used for hirsutism scoring. The same physician reported the mFG scores after inspection 9 different body areas (upper lip, chin, chest, upper arms, upper abdomen, lower abdomen, upper back, lower back, and thigh), graded from 0 to 4 (0: no hair development, 1: vellus hair development, 2: terminal hair development less than 10, 3: limited, terminal hair development more than 10; 4: frankly virile). The total score was obtained by adding the scores from all domains. The grouping was made as mild hirsute for the score of 8-15, moderate for 16-25 and severe for >25 [2,9,12]. The venous blood sample was taken from each participant prior to the administration of any medication on the 2nd or 3rd day of their menstrual cycle.

Serum Follicle Stimulating hormone (FSH), Luteinizing hormone (LH), Total testosterone (tT), Sex hormone-binding globulin (SHBG), Prolactin (PRL), Estrogen (E2), Dehydroepiandrosterone sulphate (DHEA-S), Free thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) levels were determined using commercially available assay kits (Beckman Coulter) and an autoanalyzer (Access Dxi800; Beckman Coulter Diagnostics, CA, USA). FSH, LH, tT, PRL, FT4 and TSH assay are two-site immunoenzymatic ("sandwich") assay, whereas E2 and DHEA-S assays are a competitive binding immunoenzymatic assay. 17-Hydroxyprogesterone (17-OHP) and androstenedione (A) levels were determined using commercially available assay kits (DiaMetra, segrate, ITALY) and an autoanalyzer (Etitmax 3000, DiaSorin, MN, USA). The coefficient of variation (CV) is <10 % for these assay.

Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: [(fasting glucose (mg/dl)*fasting insulin (IU/mL)*0.055)/22.5]. The adenocorticotropin (ACTH) stimulation test was performed in cases who had >2ng/ml serum 17-OHP value in the mid-follicular phase with a single intravenous bolus of 0.25 mg synthetic ACTH (Synacthen, Ciba, Basel, Switzerland) at 09:00. Blood sampling was taken at 30 and 60 minutes after ACTH injection, for determination of serum 17-OHP level. The cases with peak 17-OHP level between 4-10 ng/ml and above 10 ng/ml were classified as heterozygote congenital adrenal hyperplasia (HCAH) and non-classical CAH (NCAH) respectively [7,13].

Toshiba Apio 300 ultrasound system was used by the same radiologist for pelvic ultrasound (US) examinations. Ovarian volume was calculated with the formula used for a three-dimensional ellipsoid organs (0.5 x length x width x thickness). The cases were divided into four main groups.

1) In the idiopathic hirsutism group (Group 1), the cases with regular menstrual cycle history and normal serum androgenic level were included [8].
2) In the identification of the cases with PCOS (Group 2), the following criteria were used: a) Menstrual irregularity (oligo-menorrhea at least 2 years following menarche), b) Hyperandrogenism; clinical (acne and alopecia) or biochemical (serum tT >0.58 ng/mL or DHEAS >244 ug/dL) findings, c) Polycystic...
ovaries with increased volume (>10 ml) [6].

3) In the adrenal hirsutism (AH) group (Group 3), cases defined as heterozygote CAH and NCAH according to the ACTH stimulation test were included.

Statistics
All data were analyzed using SPSS 15.0 (Inc, Chicago, IL, USA). Parametric analysis was used for variables demonstrating normal distribution and non-parametric test for those with the non-uniform distribution. Student’s t test was used for analyses. A p value of < 0.05 was regarded as statistically significant.

Results
The mean age of the 174 hirsutic adolescents were 15.4±1.5 (11.2-18) years. The distribution of the patients in the diagnosis groups were 51 (29.3%) in group 1 (IH), 100 (57.4%) in group 2 (PCOS), and 23 (13.3%) in group 3 (AH). There was not a statistically significant difference between mean ages, hair development onset and menarche age of the groups (Table 1).

As a result of mFG scoring, mild hirsutism, moderate hirsutism and severe hirsutism were evaluated in 132 cases, 39 cases and 3 cases respectively (Table 3). The higher mFG score (14.5±4.4) was detected in group 3. mFG score was significantly different between groups. Maximum hair development was observed at the thigh, upper arm and lower back areas while minimum hair development was observed at the chest, upper abdomen, and upper back areas (Table 4/Figure 1).

The menstrual irregularity was determined higher significant in group 2 (p<0.05). There was no significant difference in family history of hirsutism between the groups (p>0.05), (Table 1). BMI sds was detected statistically significant difference between groups (p<0.05) (Table 1). Obese cases was higher in group 2. The total percentage of overweight and obese patients were (n: 77) 77% in group 2 (Table 2).

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From the laboratory findings, serum basal and average 17-OHP, DHEAS and tT levels were determined significantly higher in group 3 and LH and LH/FSH ratio were significantly higher in group 2. SHBG level were statistically lower in group 2. No significant intergroup difference was determined in terms of A, FSH, E2, PRL, fT4, TSH and HOMA-IR (p>0.05) (Table 5).
Discussion

Hirsutism is the result of either androgen excess or increased activity of the hair follicles to normal range of androgens. PCOS is the most common reason of the androgen excess and hirsutism in women. The etiology of hirsutism in adolescent girls has been reported as similar to adults [1,8,14]. In the current study, the incidence of PCOS among hirsute adolescent girls determined as 54.6%. This detection is similar to that in Ulhuhiçcar et al. [15] report on Turkish women, showing 58.2% PCOS. Noorbala et al. [16] found 60.8% PCOS in the Iranian hirsutic adolescent girls. In another reports, PCOS detected among hirsitic patients 62.5% in Iran and 91% in the United Arab Emirates [17,18]. PCOS include menstrual irregularity, hirsutism, acne, obesity and insulin resistance in women [4]. Existence of acne and mild hirsutism detected physiological during pubertal period. Moreover, physiological menstrual irregularity and insulin resistance may be seen in adolescent girls during the first two years. So, diagnosis of PCOS in adolescent girls may be problematic [10]. In current study, we diagnosed menstrual irregularity and obesity significantly higher in the PCOS group.

Adrenal enzyme disorders are another reason of androgen excess in women [1]. Heterozygosity of 21-OHD may cause functional adrenal hyperandrogenism whereas, NCAH has become an increasingly recognized cause of the hirsutism and/or menstrual dysfunction [13,19]. Moreover, PCOS-like clinical findings and US images can be occur by hyperandrogenism in the adolescent girls with NCAH. Distinguishing the both two disorders clinically is difficult. Presence of oligomenorrhea and LH/FSH ratio>2 may use exclude the PCOS [20]. In the current study, SHBG level was detected significantly higher in AH while LH/FSH ratio were higher in PCOS.

Akinci et al. [21] reported that the incidence of NCAH due to the 21-OH deficiency was 3.1% in the hirsutic adolescent. In the current study, 13.2% of hirsutic adolescent girls were evaluated in the adrenal hirsutism group. HCAH and NCAH were detected as 17 (9.8%) and 6 (3.4%) cases respectively after ACTH stimulation test. The menarche age in girls with NCAH may be seen normal or, delayed. Also, hyperandrogenism is likely to cause secondary amenorrhea [16]. We detected menstrual irregularity 30% of cases in AH group. Mean menarche age of AH group was similar to the Turkish girls data [22].

Regular ovulation with normal androgen level is defined at idiopathic hirsutism. It may be associated with androgen receptor gene polymorphisms. Aromatase and 5-alpha reductase enzyme activity disorders have been postulated to explain the pathogenesis of IH which is relatively common in Middle East-rend countries [8,14]. It has been reported as 11% among Saudi females, and 28.9% among Iranian adolescent girls [16,23]. In the present study, the related percentage of IH was determined 25.6% as the second most common reason of adolescent hirsutism with a high ratio of mild hirsutism.

Visual methods of determining the severity of hirsutism were usually defined by Ferriman and Gallwey. The clinically convenient mFG scoring system is frequently used [9]. Coskun et al. [2] reported that mild and moderate mFG scores were 74.4% and 11.6% respectively with PCOS in adults. In the current study, we detected mild hirsutism as higher range (75.9%) while moderate hirsutism was 22.4% in all groups. The hair follicles on the body are known to be androgen sensitive at different degrees. The most sensitive facial areas chin, under the jaw and upper lip. Most sensitive body areas are the pubic area, upper thighs, linea alba and chest [24]. In this study, maximum scores were determined in the thigh, upper arm and the lower back areas. The scores of the upper lip, chin and lower abdomen were close to each other. In the study of Hassa et al. [25] on FG scoring of 11 body areas, higher scores were determined at the thigh and lower back areas similar to the present study. The low FG score they have determined at the upper back, upper abdomen and chest areas was similar to our mFG score values. Interestingly, although upper lip is one of the facial areas that is the most sensitive to androgens has got a low FG score in both studies. It may be explained with the epilation applied to that area frequently. In a study, upper lip area was identified as the area with the maximum inter-personal variety among the people being examined, although moustache is an area that is highly sensitive to androgens. It was determined as below average with a kappa value of 0.585 and it was stated that the hirsutism diagnosis should be society specific.

In conclusion, this study suggests that PCOS is the most frequent reason of hirsutism for the adolescent age group that is generally showing menstrual irregularity, mild hair growth and obesity. These may main reasons for application to clinics earlier in adolescents with PCOS. Therefore, in the adolescents with a distinctive diagnosis of hair development whose menstruation is regular, firstly idiopathic hirsutism or adrenal hirsutism can be thought. In Turkish society with a higher incidence of hirsutism, a preunderstanding of hirsutism can be obtained by firstly examining upper thigh, lower back, upper arm and chin areas. On the other hand, upper lip area's being a site where frequent epilation is applied may be deceptive concerning scoring.

Competing interests

The authors declare that they have no competing interests.

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