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Screening Patients with Polycystic Ovary Syndrome for Cushing's Syndrome

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Abstract
Objective: Polycystic ovary syndrome (PCOS) and Cushing's syndrome share several clinical features such as hirsutism, irregular menses, obesity, glucose intolerance and dyslipidemia. The aim of this study was to investigate the presence of Cushing's syndrome in patients who were admitted with the complaints of hirsutism and/or irregular menses and were diagnosed with PCOS.
Material and Methods: One hundred nine patients with PCOS (aged 14-35 years) were included in the study. We evaluated anthropometric, hormonal, and metabolic parameters. All the patients were evaluated with 1-mg dexamethasone suppression test (DST) for Cushing's syndrome.
Results: The mean body mass index of the patients was 35.6 ± 9.5 kg/m^2 and 75.2% of the patients were obese. The mean Ferriman-Gallwey score of the patients was 12.6 ± 3.7 and 61.1% of them had menstural irregularities. While the mean fasting plasma glucose level of the patients was 96.5 ± 12.8 mg/dl, mean value of HOMA-IR was 3.2 ± 1.9. We observed HOMA-IR>2.7 in 52.3% of the patients. Three patients failed to suppress plasma cortisol following1 mg- dexamethasone administration. Then, we performed 2-day 2 mg DST and observed that all the three patients suppressed cortisol levels to less than 1.8 µg/dl. In patients with severe hirsutism (n=34) the average 1-mg DST result was 0.73 ± 0.7 mg/dL in patients with mild and moderate hirsutism (n=75), however, this value was 0.64 ± 0.4 mg/dL (p=0.427).
Conclusion: We did not observe Cushing's syndrome in the young women who were diagnosed with PCOS.
Key Words: Polycystic Ovary Syndrome; Cushing's Syndrome; 1 mg- Dexamethasone Supression Test.

Polikistik Over Sendromu Tanılı Hastaların Cushing Sendromu Açısından Taranması

Özet
Amaç: Polikistik over sendromu (PKOS) ve Cushing sendromu hirsutizm, menstrual düzensizlik, obezite, glukoz intoleransı, dislipidemi gibi birçok ortak klinik bulguya sahiptir. Bu çalışmanın amacı hirsutizm ve/veya menstrual düzensizlik nedeniyle başvuran ve PKOS tanısı koyduğumuz hastaları Cushing sendromu açısından taramaktır.
Gereç ve Yöntemler: Çalışmaya PKOS tanısı koyduğumuz, yaşları 14-35 arasında değişen 109 hasta dahil edildi. Tüm hastalarda antropometrik, hormonal ve metabolik ölçümler yapıldı. Cushing sendromu açısından tüm hastalara 1 mg- deksametazon supresyon testi (DST) uygulandı.
Bulgular : Hastaların ortalama beden kitle indeksi ölçümleri 35.6± 9.5 kg/m^2 olup, hastaların %75.2'sini obez grup oluşturuyordu. Hastaların ortalama Ferriman- Gallwey skoru 12.6 ± 3.7 olup, %61.1'inde menstrual düzensizlik mevcuttu. Hastaların ortalama açlık plazma glukoz düzeyleri 96.5 ± 12.8 mg/dl iken, ortalama HOMA-IR değerleri 3.2± 1.9 olarak saptandı. Hastaların %52.3'ünde HOMA-IR>2.7 olarak bulundu. Hastalar 1 mg DST ile tarandığında; sadece 3 hastada kortizol düzeylerinde supresyon olmadı. Daha sonra üç hastaya da 2 gün 2 mg DST uygulandı ve her üç hastada da kortizol düzeylerinin 1.8 µg/dl'nin altına indiği görüldü. Ciddi hirsutizmi olan hastalarda (n=34) ortalama1-mg DST değeri 0.73 ± 0.7 mg/dL idi; fakat hafif ya da orta düzeyde hirsutizmi olan hastalarda bu değer 0.64 ± 0.4 mg/dL olarak saptandı (p=0.427).
Sonuç: Polikistik over sendromu tanısı koyduğumuz genç kadınların hiçbirinde Cushing sendromu saptanmadı.
Anahtar Kelimeler: Polikistik Over Sendromu; Cushing Sendromu; 1 mg- Deksametazon Supresyon Testi.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disease that affects 6-10% of women in their reproductive age (1). It is characterised by irregular menstruation, chronic anovulation, infertility, and hyperandrogenism (2). Patients with PCOS are at increasing risk of metabolic disorders like abdominal obesity, insulin resistance, hyperinsulinism, type 2 diabetes, dyslipidemia, and cardiovascular diseases (3-5). To be able to diagnose PCOS, other diseases that cause hyperandrogenism and ovulatory dysfunction should be left out (6). One of these diseases is Cushing's syndrome (CS).

Polycystic ovary syndrome and Cushing's syndrome share many common clinical features (7). Central obesity is an important clinical finding for CS and 40 to 60% of PCOS patients are either overweight or obese (8). In

analogy with PCOS, patients with Cushing's syndrome may have hirsutism, menstrual irregularities, acne, and infertility (7,9). Moreover, hypertension and glucose intolerance are also among common symptoms in patients with CS.
To be able to make a differential diagnosis between the two diseases in subclinical cases lacking traditional CS signs, there is need to apply hormonal tests (10). As an easy-to-apply and inexpensive test, 1-mg dexamethasone suppression test (DST) is often used at clinics as the first step of screening (11).

Patients with polycystic ovary syndrome can be treated medically. However, surgery is the primary treatment for CS. Therefore, it is very important to distinguish between the two diseases. In addition, early diagnosis of CS reduces morbidity and mortality (12).

Our aim in this study was to examine the outpatients, who had applied to our clinic for hirsutism and/or menstrual irregularities and, eventually, diagnosed with PCOS, for Cushing's syndrome by using 1-mg dexamethasone suppression test.

MATERIAL AND METHODS

The study was carried out with patients diagnosed with PCOS according to Rotterdam diagnostic criteria (13) at the Endocrinology and Internal Medicine Outpatient Clinic, Faculty of Medicine, Recep Tayyip Erdogan University. Rotterdam diagnostic criteria require the following conditions for the diagnosis of PCOS: i) oligo or anovulation; ii) clinical (hirsutism, acne, male pattern hair loss) or biochemical findings for hyperandrogenism; iii) having two of the polycystic ovary appearance criteria in ultrasonography and eleminating other reasons for hyperandrogenism (2). Hirsutism was evaluated according to the Ferriman-Gallwey (FG) score. FG score above 8 is defined as hirsutism (14).

We excluded all tumours secreting androgen, hyperprolactinemia and congenital adrenal hyperplasia. The exclusion criteria were exogenous glucocorticoid use, serious diseases that could affect pituitary-adrenal axis, conditions that could affect dexamethasone suppression test (antiepileptic drugs, oestrogen use, alcohol abuse, depression and other psychiatric conditions, pregnancy), and renal insufficiency (creatinine clearance <30 mL/min).

We collected the data concerning weight, height, waist circumference, and blood pressure measurements. Body mass index (BMI) was calculated in kilograms by dividing body weight (in square meters) by height (in centimetres) (kg/m2). Waist circumference was measured from the midpoint of the distance between arcus costarum and anterior superior iliac spine. All patients were evaluated for acne, acanthosis nigricans, and androgenic alopecia.

Biochemical and hormonal measurements

After an 8-12 hours of fasting, 08:00 in the morning, we collected venous blood samples from all patients in the follicular phase of the menstrual cycle. Urea, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), and insulin levels were measured. We performed 75 g oral glucose tolerance test (OGTT) for all patients. To calculate the insulin resistance, we used the following formula: homeostasis model assessment-insulin resistance (HOMA-IR)= fasting plasma glucose (mmol/L) × fasting serum insulin (mU/mL) / 22.5 (15). The threshold value for HOMA-IR was 2.7 (16).

To measure the glucose levels, we used the hexokinase method, for the lipid level measurements, on the other hand, we relied on the photometric method (Abbott Architect c16000). Insulin levels were calculated by using CMIA method (Chemiluminescent microparticle immunoassay) (Abbott Architect system, USA).

We used CMIA method (Abbott Architect i2000, USA) to measure serum FSH, LH, estradiol, prolactin, dehidroepiandrostenodio-sulfate (DHEAS), total testosterone, and TSH levels. For serum 17-hydroxyprogesterone (17-OHP) levels, however, we used the radioimmunoassay (RIA) method.

We performed 1-mg dexamethasone suppression test (DST) to all patients after evaluating their basal cortisol and ACTH levels. To apply the 1 mg-DST test, we asked the patients to have 1 mg of dexamethasone orally at 23:00; at 08:00 am, we checked serum cortisol levels. Levels under 1.8 mg/dl were taken the suppressed cortisol value for 1 mg of DST. Patients with >1.8 mg/dL serum cortisol after the 1-mg DST administration were applied 2 mg DST for 2 days. To do this, the patients orally took 0.5 mg of dexamethasone every six hours for two days. 6 hours after the last dose, at 8:00 in the morning, we measured their serum cortisol levels and <1.8µg/dl was considered as the normal suppression level.

We used SPSS 19.0 software (SPSS, Chicago, IL, USA) for the statistical analysis. The results were evaluated as mean ± standard deviation.

RESULTS

With ages ranging from 14-35, 109 patients were included in the study. The mean BMI of all the patients was 35.6 ± 9.5 kg/m^2 and 75.2% of them were obese. The mean FG score was 12.6 ± 3.7 and 61.1% of the patients had menstrual irregularities. Clinically, 67% of the patients had acne while 51.4% had androgenic alopecia and 56% had acanthosis nigricans. Pelvic ultrasonography showed polycystic ovary appearance in 57.4% of the patients. The demographic and clinical characteristics of the patients are provided in Table 1.

The mean fasting plasma glucose levels of our patients was 96.5 ± 12.8 mg/dl and the mean HOMA-IR value was determined as 3.2 ± 1.9. In 52.3% of the patients, we detected HOMA-IR as >2.7. OGTT results of the patients showed impaired fasting glucose (IFG) in 21.2%, impaired glucose tolerance (IGT) in 5.8%, both IFG and

IGT in 4.8%, and type 2 diabetes in 4.8% of them. Moreover 18% of the patients had hyperlipidemia.

Table 1. Demographic and clinical characteristics of the patients.

Parameters	Mean±SD
Age	24.6 ± 7.2
BMI (kg/m^2)	35.6 ± 9.5
Systolic blood pressure (mmHg)	128.1 ± 16.5
Diastolic blood pressure (mmHg)	78 ± 13.5
Waist circumference (cm)	104.7 ±17.5
Ferriman-Gallwey score	12.6 ± 3.7
Acnes (%)	%67
Androgenic alopecia (%)	%51.4
Acanthosis nigricans(%)	%56
Oligomenorrhea/amenorrhea (%)	%61.1

The mean LH/FSH ratio was 1.1 ± 1 and the estradiol level was 44.2 ± 33.2 pg/ml. Hormonal measurements of patients are shown in Table 2.

Table 2. Biochemical and hormonal resuts of the patients.

Parameters	Mean± SD
Fasting plasma glucose (mg/dl)	96.5 ± 12.8
Fasting insulin (µIU/ml)	13.3 ± 7.5
HOMA-IR	3.2 ± 1.9
Total-cholesterol (mg/dl)	203.8 ± 40.7
Triglyceride (mg/dl)	126.3 ± 61.2
LDL- cholesterol (mg/dl)	128.1 ± 32.8
HDL- cholesterol (mg/dl)	47.1 ± 11.5
Free T4 (ng/dl)	1.1 ± 0.1
TSH (µIU/ml)	2.5 ± 1.6
Basal cortisol (µg/dl)	11.2 ± 4.5
ACTH (pg/ml)	17.4 ± 13.5
FSH (mIU/ml)	4.7 ± 1.5
LH (mIU/ml)	5.2 ± 3.7
Estradiol (pg/ml)	44.2 ± 33.2
Prolactin (ng/ml)	18 ± 15.3
Total testosterone (ng/ml)	0.7 ±0.3
DHEAS (µg/dl)	251.4 ± 123.6
Free testosterone (pg/ml)	3.9 ± 6.01

1-mg DST test for CS showed values ranging from 0.1 to 3.5 mg/dL and the average value was 0.66 ± 0.5 mg/dL. This value was found to be below 1 mg/dL in most patients (96/109). Only 3 patients did not show suppression of cortisol levels after 1-mg of dexamethasone application. Then, we administered 2 mg of dexamethasone as a part of the suppression test to these three patients and all three patients reacted to the test by showing cortisol levels below 1.8 mg/dL. The clinical findings of these three patients are worth to mention; two of them were obese patients with insulin resistance while the other was lean and did not have any insulin resistance. All three had a FG score of >16 and had menstrual irregularities while only two of them had LH/FSH ratio above 2. Again only two of these patients had a polycystic ovarian appearance on ultrasound, while the other patient was free of this condition.

In patients with severe hirsutism (n=34) the average 1-mg DST result was 0.73 ± 0.7; in patients with mild and moderate hirsutism (n=75), however, this value was 0.64 ± 0.4. The statistical difference between them was insignificant (p=0.427). The same conclusion also applies to the relationship between the patients with menstrual irregularities (0.64 ± 0.4) and those without menstrual irregularities (0.69 ± 0.6) (p=0.587). On the other hand, the difference between the patients with polycystic ovarian issues in the ultrasonography (0.59 ± 0.3) and those without such an appearance (0.7 ± 0.84) was statistically significant (p=0.025).

Handling the matter by grouping the patients as obese (0.65 ± 0.5) and non-obese (0.71 ± 0.6) after the 1-mg DST, we found out that there was, again, no notable difference between the groups (p = 0.653). Still, there was not any statistically significant difference between the patients with HOMA-IR values over 2.7 (0.69 ± 0.4) and those with HOMA-IR values below 2.7 (0.61 ± 0.6) (p=0.433). In 51 patients with LH/FSH ratio >2, the mean 1-mg DST value was 0.69 ± 0.6, while in 58 patients with LH/FSH ratio <2 the average 1-mg DST value was 0.70 ± 0.5 (p=0.945).

DISCUSSION

In this study, we could not detect Cushing's syndrome in any of the patients who had applied to our clinic with hirsutism and/or menstrual irregularity complaints and been diagnosed with polycystic ovary syndrome.

Although polycystic ovary syndrome is seen in 6-10% of women in their reproductive ages, classical Cushing's syndrome is rather rare. The incidence rate of Cushing's syndrome in European countries is reported to be 0.7-2.4 per million (17).

PCOS constitutes the majority of hirsutism cases. For the diagnosis of PCOS, other diseases causing hyperandrogenism and ovulatory dysfunction should be eliminated according to the Rotterdam diagnostic criteria (6). CS is one of these diseases, but it rarely emerges as a cause of hirsutism. In a study on 340 patients who were evaluated for hirsutism, it has been reported that only one of them had CS (18). In a study conducted recently in Turkey, there were not any CS cases among 105 patients with hirsutism (19). In our study, hirsutism was present in all the patients but we could not detect CS in any of our patients.

Hirsutism and menstrual irregularities are common clinical findings in CS. In a study conducted on patients with CS only, it was discovered that 70% of these patients had menstrual irregularity complaints while all of them had at least one clinical findings related to hyperandrogenism. The same study reveals that the ultrasound results displayed polycystic ovaries in 46% of the patients (20).

PCOS and CS are in common in clinical findings such as central obesity, glucose intolerance, hypertension, and dyslipidemia. However, none of these findings are specific to CS or PCOS. Because CS-specific clinical findings such as purple abdominal striae wider than 1 cm and proximal muscle weakness are not to be found

especially in subclinical CS cases, may be difficult to distinguish PCOS from CS.

1-mg dexamethasone suppression test is one of the recommended the initial screening tests in CS by the European Society of Endocrinology (9). In this study, we also used 1-mg DST. In some studies, it has been reported that 1-mg DST has achieved a suppression rate of 2-8% in obese patients (11, 21, 22). In PCOS, there may be moderately increased cortisol excretion due to changes in hypothalamic-pituitary-adrenal axes (23-25) which may prevent the suppression by 1-mg DST. In Putignano et al's study, the CS screening of obese female patients was carried out by applying urine cortisol, evening cortisol, and 1-mg DS tests. As a result, they have concluded that 1-mg DST qualifies as a safe screening test though doctors should be tactful in interpreting the test results of patients with high levels of moderate urinary cortisol (24). In our study, we were unable to detect suppression in cortisol levels of 3 patients after 1-mg DST. It was only when we applied 2-mg DST, we observed suppression in cortisol levels in these 3 patients. Because we did not evaluate our patients in term of urinary cortisol or late night cortisol tests, we could not compare these tests with 1-mg DST. However, because none of the patients included in this study had any CS-specific findings, we concluded that our 1-mg DST results have been coherent and could be used as an initial screening test. 1-mg DST results were found to be similar among all patients when they were divided into subgroups according to hirsutism scores, menstrual patterns, obesity, insulin resistance, and LH/FSH ratios. However, the mean 1-mg DST values were lower in patients with polycystic ovaries according to their ultrasound results. According to these findings, we can safely claim that there is no need to apply CS screening for patients with PCOS but without any CS-specific findings.

As a result, it can be stated that although guidelines suggest that Cushing's syndrome, one of the reasons of hyperandrogenism, should be excluded to diagnose patients with PCOS, it is not a common clinical condition. CS screening in patients with PCOS should be limited to patients with clinical signs specific for CS and to those who do not answer to PCOS treatment.

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