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Original Article

Autonomic dysfunction in patients with polycystic ovary syndrome

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ABSTRACT

Objective: To assess the autonomic system in patients with polycystic ovary syndrome (PCOS).
Materials and methods: Thirty-seven adult patients with PCOS and 33 healthy controls were enrolled in the study. The electrophysiological assessments of the autonomic nervous system function were performed using sympathetic skin response and R–R interval variation tests.
Results: The mean latency of sympathetic skin response in PCOS patients was significantly delayed compared with the controls ($p = 0.001$). The mean amplitude of sympathetic skin response was significantly lower in comparison with the controls ($p = 0.01$). Mean R–R interval variation during deep breathing was also significantly delayed ($p = 0.04$).
Conclusion: There are parasympathetic dysfunction and sympathetic dysfunction in patients with PCOS. This may be easily demonstrated with sympathetic skin response and R–R interval variation tests.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It occurs in about 6–10% of women [1,2]. Despite decades of research, the complex pathogenesis of PCOS remains incompletely understood. The symptoms of PCOS are amenorrhea, oligomenorrhea, hirsutism, obesity, infertility, anovulation, and acne. The disease can lead to marital and social maladjustment and can impair sexual functioning [3]. According to the Rotterdam Criteria, PCOS is diagnosed in the presence of at least two of three criteria: menstrual disorders or amenorrhoea with chronic lack of ovulation, clinical and/or biochemical features of hyperandrogenism, and the presence of polycystic ovaries in ultrasonography after the exclusion of other endocrine disorders [4].

PCOS is an important metabolic disorder, as women with PCOS may have significant insulin resistance, glucose intolerance, obesity, hypertension, and dyslipidemia. Adrenergic overactivity leads to the formation of these factors. Adrenergic overactivity is an important prognostic factor for the development of cardiovascular disorders [5–7]. Previous studies indicated that the ANS plays an important role in the regulation of ovarian physiology [8]. Few reports showed the role of increased sympathetic activity in patients with PCOS [9,10]. Autonomic dysfunction has also been reported to be associated with adverse cardiovascular events [11].There is a relationship between the ANS and cardiovascular mortality [12].

To our knowledge, there are no studies to date evaluating the relationship between the ANS and PCOS using electromyography (EMG) in current literature. The present study was conducted to assess the ANS in patients with PCOS using sympathetic skin response (SSR) and R–R interval variation (RRIV) tests in EMG.

Materials and methods

Thirty-seven adult patients with PCOS and 33 healthy controls who were referred to the Kirikkale University Gynecology Clinic, Kirikkale, Turkey were enrolled in the present study, PCOS was diagnosed according to the Rotterdam Criteria. Age-matched, healthy, regularly menstruating, and nulliparous women were included as controls. Women with menstrual irregularities, hypothyroidism, diabetes, and women on any hormonal therapy or drugs were excluded. The study was approved by the Kirikkale University local ethic committee. All research procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent/permission was obtained from all parent participants.

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Specification of phenotypes was proposed in a workshop convened by the National Institutes of Health (NIH) in 2012 [13]. There are four phenotypes. Phenotype 1 (classic PCOS) includes clinical and/or biochemical evidence of hyperandrogenism and hyperandrogenism, evidence of oligoanovulation, and ultrasonographic evidence of a polycystic ovary. Phenotype 2 (hyperandrogenic anovulation) includes clinical and/or biochemical evidence of hyperandrogenism and evidence of oligoanovulation. Phenotype 3 (ovulatory PCOS) includes clinical and/or biochemical evidence of hyperandrogenism and hyperandrogenism, and ultrasonographic evidence of a polycystic ovary. Phenotype 4 (non-hyperandrogenic PCOS) includes evidence of oligoanovulation and ultrasonographic evidence of a polycystic ovary. We classified our patients according to these classifications.

Demographic characteristics including age and body mass index (BMI) were recorded.

A detailed neurological examination was performed, and clinical autonomic symptoms including feeling faint on orthostatic change of posture, distal vasomotor dysfunction, sweating abnormalities, and gastrointestinal, genital, or urinary disorders were recorded in all participants. Individuals with neurological findings and autonomic symptoms were not included in the study.

Electrophysiological assessments

The electrophysiological assessments of ANS function were performed using SSR and RRIV, which were recorded according to the methods described Shahani et al [14,15]. All participants were studied in the supine position using the equipment Carefusion Synergy (CareFusion, USA) by the same physician (MA). All study sessions were completed in the morning at least 2 hours after a light breakfast in a quiet semidarkened room with an ambient temperature of between 23°C and 26°C ,and an extremity skin temperature over 31°C.

RRIV was used for parasympathetic function and was recorded using disk electrodes placed on the chest wall across the cardiac position with a ground electrode on the right axial line at the lowest rib. Using the triggering mode and adjusting, the sweep speed two QRS (mainly R waves) of electrocardiography were simultaneously displayed on the screen. Because the first displayed complex represented the triggering potential, the variation in timing of the second complex represents the variation in the R–R interval. Twenty traces were recorded and superimposed, and a printout was made for subsequent measurement. Five groups of 20 sweeps were recorded at rest and two during forced deep breathing at six breaths per minute. The band pass was 20–100 Hz, the sensitivity 0.2 mV, and the sweep duration was 0.2–1 seconds. The range in the 20 pairs of R– R intervals was termed as (a), and the mean R–R interval was termed as (b). The RRIV was expressed as a percentage of the average R–R interval using the formula RRIV = a/b × 100 [14,15]. The recordings and calculations were performed with computer software (SPSS 16, SPSS Inc., Chicago, IL, USA). RRIV responses at rest and deep breathing were considered abnormal when they were more than two standard deviations (SD) lower than mean responses, age-adjusted for a normal population [16].

SSR was used to measure sympathetic function. SSR recordings were performed using disc electrodes attached to the palm and dorsum of the right hand. The same device and electrical stimuli were used, and single square wave pulses of 0.1 seconds duration and 10–20-mA intensity were applied to the dominant median nerve at the wrist portion. Latency and amplitude of the response were analyzed. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured peak to peak [14,15].

Response latencies were considered pathological when they were more than two SD above the mean latency of the control group.

Statistical analysis

All parameters were expressed as mean ± SD, as well as percentages (for categorical variables). The patients and healthy controls were compared using a one-way analysis of variance for continuous parameters and Chi-square test for categorical parameters. Bivariate analyses were performed using Pearson correlation. A p value < 0.05 was considered to be statistically significant.

Results

The baseline clinical characteristics of patients with PCOS and controls are shown in Table 1. Phenotypic presentation of patients with PCOS are shown in Table 2. No statistically significant difference was found between the patient and the control groups in terms of age ($p = 0.58$). There was a slight statistically difference between both groups in BMI ($p = 0.05$). Patients with PCOS had significantly higher levels of testosterone and insulin than that of healthy controls (respectively; $p = 0.01$, $p = 0.02$).

Right hand SSR latency was found to be 1.37 ± 0.52 ms in the patients and 0.86 ± 0.30 ms in the controls; right hand SSR amplitude was 0.59 ± 0.53 mV in the patients and 1.13 ± 0.65 mV in the controls. The mean latency of SSR in the patients was significantly delayed, compared with the controls ($p = 0.001$). The mean amplitude of SSR in the patients was significantly lower, compared with the controls ($p = 0.01$).

Mean RRIV at rest was detected to be 91.22 ± 54.25% in patients and 87.06 ± 49.08% in controls. Mean RRIV during deep breathing was detected to be 112.28 ± 56.50% in the patients and 87.30 ± 42.51% in the controls. No statistically significant difference was found between the patients and the controls in RRIV at rest ($p = 0.73$). Mean RRIV during deep breathing was significantly delayed, compared with the controls ($p = 0.04$). There was no relationship between RRIV, age, and BMI (Table 3). There was no relationship between SSR, age, and BMI (Table 4).

Discussion

We investigated autonomic dysfunction in patients with PCOS in this present study. In this study, both sympathetic systems and parasympathetic systems were evaluated with SSR and RRIV. SSR

Table 1
Baseline characteristics of the study population.

Variables	Patients ($n = 37$)	Controls ($n = 34$)	p
	Mean ± SD	Mean ± SD	
Year (y)	21.56 ± 3.37	21.20 ± 1.85	0.58
Body mass index (kg/m^2)	22.62 ± 3.66	21.02 ± 3.22	0.05
Total cholesterol (mg/dL)	167.97 ± 28.36	163.84 ± 16.83	0.46
HDL cholesterol (mg/dL)	61.27 ± 11.52	58.24 ± 9.21	0.23
LDL cholesterol (mg/dL)	97.86 ± 21.46	94.48 ± 18.92	0.48
Triglyceride (mg/dL)	84.72 ± 39.13	74.06 ± 26.56	0.19
Blood glucose (mg/dL)	92.62 ± 9.16	89.54 ± 6.97	0.12
FSH (IU/L)	5.26 ± 1.63	5.60 ± 1.65	0.40
LH (IU/L)	10.07 ± 5.32	8.57 ± 3.69	0.18
Estradiol (pg/mL)	50.22 ± 7.60	46.94 ± 15.07	0.26
Testesterone (ng/mL)	0.49 ± 0.17	0.41 ± 0.11	0.01
DHEAS (mcg/dL)	282.59 ± 100.89	251 ± 77.90	0.15
Insulin (IU/mL)	11.15 ± 3.95	8.87 ± 3.80	0.02

DHEAS = dehydroepiandrosterone; FSH = follicle stimulating hormone; HDL = high density lipoprotein; LDL = low density lipoprotein; LH = luteinizing hormone.