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Hormonal abnormalities in first-degree relatives of women with polycystic ovary syndrome (PCOS)

Zaburzenia hormonalne u krewnych pierwszego stopnia kobiet z zespołem policystycznych jajników (PCOS)

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Abstract

Introduction: A body of evidence points to a familial aggregation of hormonal abnormalities in first-degree relatives of women with polycystic ovary syndrome (PCOS).
The aim of this study was to determine whether siblings of women with PCOS had evidence of hormonal abnormalities typical of PCOS.
Material and methods: Eighty-six siblings of women with PCOS (44 sisters, 42 brothers) were recruited. Two control groups consisted of 70 healthy women and 30 healthy men. Anthropometric, hormonal (testosterone, androstenedione, DHEA-S, LH, FSH) parameters and SHBG were assessed in all subjects.
Results: Mean testosterone and DHEA-S levels were higher in sisters of women with PCOS than in the control women. In eight of the 44 (18.2%) sisters, a diagnosis of PCOS was made. Mean testosterone and androstenedione levels, and free androgen index (FAI) were significantly higher in sisters with PCOS compared to the sisters without PCOS. Brothers of women with PCOS had higher DHEA-S level than the control men. Eleven of the 42 (26.2%) brothers had alopecia occurring before the age of 30. Prematurely balding brothers did not differ from the non-balding brothers in hormonal parameters.
Conclusions: Siblings of women with PCOS are predisposed to hormonal abnormalities typical of PCOS. The symptom of premature balding under the age of 30 in brothers of women with PCOS should not be considered as a male PCOS equivalent.
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Key words: *polycystic ovary syndrome (PCOS), siblings, familial occurrence, hormonal disturbances*

Streszczenie

Wstęp: Liczne dane wskazują na rodzinne występowanie zaburzeń hormonalnych u krewnych pierwszego stopnia kobiet z zespołem policystycznych jajników (PCOS, *polycystic ovary syndrome*).
Celem pracy była ocena czy u rodzeństwa kobiet z PCOS występują zaburzenia hormonalne typowe dla tego zespołu.
Materiał i metody: Zbadano 88 krewnych pierwszego stopnia kobiet z zespołem wielotorbielowatych jajników (44 siostry i 42 braci). Grupy kontrolne stanowiło 70 zdrowych kobiet i 30 zdrowych mężczyzn. U wszystkich osób oceniono parametry antropometryczne i hormonalne (stężenia testosteronu, androstendionu, DHEA-S, LH, FSH) oraz stężenie SHBG.
Wyniki: Średnie stężenia testosteronu i DHEA-S były większe u sióstr kobiet z PCOS niż u kobiet z grupy kontrolnej. U 8 z 44 sióstr (18,2%) postawiono rozpoznanie PCOS. Średnie stężenia testosteronu, androstendionu oraz indeks wolnych androgenów były istotnie większe u sióstr z PCOS w porównaniu z siostrami bez tego zespołu. Bracia kobiet z PCOS w porównaniu z mężczyznami z grupy kontrolnej mieli większe stężenia DHEA-S. Przedwczesne łysienie cechowało 11 z 42 braci (26,2%), które wystąpiło przed 30. rokiem życia. Przedwcześnie łysiejący bracia nie różnili się od braci bez łysienia pod względem ocenianych parametrów hormonalnych.
Wnioski: Rodzeństwo pacjentek z PCOS jest predysponowane do występowania zaburzeń hormonalnych typowych dla tego zespołu. Przedwczesne łysienie u mężczyzn przed 30. rokiem życia nie powinno być uznawane za męski fenotypowy odpowiednik PCOS.
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Słowa kluczowe: *zespół policystycznych jajników (PCOS), rodzeństwo, rodzinne występowanie, zaburzenia hormonalne*

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Introduction

Polycystic ovary syndrome (PCOS) is one of the commonest endocrinopathies among young women. It is a syndrome which combines abnormal menstruation, features of androgen excess, obesity, insulin resistance, and other metabolic disturbances [1–6]. An extremely interesting issue is familial occurrence of PCOS. First-

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degree female relatives of patients with PCOS may have some features, or the full picture, of the syndrome, such as increased concentrations of testosterone, DHEA-S, androstenedione, and LH [7–9]. Interestingly, some components of the disease are also found in male relatives, such as higher concentrations of LH and DHEA-S and low SHBG levels [10–13]. What is more, a phenotypic male equivalent of PCOS, characterised by alopecia occurring before the age of 30, has been defined [11–14].

The aim of our study was to find whether brothers and sisters of patients with PCOS differ from the healthy siblings of healthy women in terms of hormonal parameters.

Material and methods

The study included 86 first-degree relatives (44 sisters and 42 brothers) of women with PCOS. The women with PCOS were patients of the Department of Endocrinology, Diabetology, and Isotope Therapy of Wroclaw Medical University. PCOS was diagnosed according to the Rotterdam criteria (two of three symptoms: 1. abnormal menstruation or absence of menstrual periods resulting from chronic oligo- or anovulation, 2. clinical and/or biochemical hyperandrogenism, and 3. a characteristic ultrasound picture of the ovaries). The control groups consisted of 70 healthy women and 30 healthy men whose sisters did not have PCOS, menstrual disturbances, or hirsutism. The control groups were formed by the students of Wroclaw Medical University. Siblings and subjects from the control groups (appropriately women and men) were matched with regard to age, body mass and BMI.

Persons eligible for the study had not been previously treated with hormonal or insulin-sensitising drugs and they stated that during the three months prior to the study they had not been on any special diet or practiced intense physical exercise. They consumed alcohol occasionally, and had not smoked more than five cigarettes a day. Subjects with hypercortisolaemia, hyperprolactinaemia, impaired thyroid function, or suspicion of ovarian or adrenal tumour were excluded from the study.

The study protocol was approved by the Ethics Committee of Wroclaw Medical University and all the subjects gave their informed consent in writing.

Physical examination

A physical examination of all the subjects was carried out, which included arterial blood pressure and anthropometrical measurements such as body mass, body height, and waist and hip circumference. Body mass index (BMI) was calculated from the equation: body mass [kg]/height-squared [m^2]. The waist-to-hip ratio (WHR) was calculated from the quotient: waist circumference [cm]/hip circumference [cm].

Laboratory tests

Blood for laboratory tests was collected between 8am and 10 am after overnight fasting, (at least eight hours since the last meal). For the women, all the tests were carried out between the 2^{nd} and 10^{th} days of a spontaneous cycle or a cycle induced by progestin.

Serum hormone concentrations (testosterone, DHEA-S, LH, FSH, oestradiol, prolactin, TSH, insulin) and SHBG were determined by a chemifluorescent method using an Immulite 2000 analyser (DPC, Diagnostic Products Corporation, Los Angeles, CA, USA). Serum androstendione was measured by a radioimmunological method using commercially available kits (DPC, Diagnostic Products Corporation, Los Angeles, CA, USA).

Based on the concentrations of total testosterone (T) and SHBG, the free androgen index (FAI) was calculated: T/SHBG × 100.

Statistical analysis

Shapiro-Wilk's test assessing the normality of the data distribution was used to evaluate the assumption of the parametric tests. To assess differences between groups, the data were analyzed by means of the Student's *t* test. In the absence of a normal distribution, the non-parametric Mann-Whitney *U* test was used. The variability of the tested features due to the group and body mass index was studied by two-factorial analysis of variance. Post-hoc comparison between groups was made with Tukey's LSD test. The level of statistical significance was set at $p < 0.05$.

Results

None of the groups of women (S_{PCOS}, CG♀) and the groups of men (B_{PCOS}, CG♂) differed significantly in terms of average age or average values of the anthropometric parameters.

Selected hormonal parameters in the group of sisters of the patients with PCOS and in the control group of women are shown in Table I. The mean concentrations of total testosterone and DHEA-S were significantly higher in the sisters of the PCOS patients than in the control group of women.

The hormonal parameters of the brothers of the PCOS patients and the male control group are summarised in Table II. Mean DHEA-S concentration was significantly higher in the brothers of patients with PCOS than in the males of the control group. In addition, the brothers showed a significantly lower mean concentration of LH and a lower mean value of the LH/FSH ratio.

Table I. *Comparison of hormonal parameters in the sisters of patients with PCOS and the control women*
Tabela I. *Porównanie parametrów hormonalnych u sióstr pacjentek z PCOS i kobiet z grupy kontrolnej*

	S_{PCOS}	CG♀	p
Testosterone [ng/mL]	0.626 ± 0.264	0.50 ± 0.196	0.00436
SHBG [nmol/L]	43.991 ± 26.264	35.635 ± 19.662	0.05626
FAI	6.396 ± 3.945	6.478 ± 4.658	ns
Androstenedione [ng/mL]	3.726 ± 1.255	3.686 ± 1.433	ns
DHEA-S [μg/dL]	244.234 ± 96.444	163.730 ± 69.369	< 0.001
LH [mIU/mL]	7.475 ± 5.452	7.360 ± 5.830	ns
LH/FSH	1.280 ± 0.861	1.226 ± 0.729	ns

S_{PCOS} — sisters of women with PCOS; CG♀ — female control group

Table II. *Comparison of hormonal parameters in the brothers of patients with PCOS and the control men*
Tabela II. *Porównanie parametrów hormonalnych u braci pacjentek z PCOS i mężczyzn z grupy kontrolnej*

	B_{PCOS}	CG♂	p
Testosterone [ng/mL]	5.994 ± 1.891	5.257 ± 1.734	0.09589
SHBG [nmol/L]	22.724 ± 7.431	23.127 ± 11.545	ns
FAI	99.234 ± 40.812	87.788 ± 26.053	ns
Androstenedione [ng/mL]	3.126 ± 0.891	3.030 ± 0.792	ns
DHEA-S [μg/dL]	310.619 ± 100.802	222.003 ± 117.022	< 0.001
LH [mIU/mL]	2.893 ± 1.239	4.240 ± 1.317	< 0.001
LH/FSH	0.884 ± 0.495	1.365 ± 0.726	0.00133

B_{PCOS} — brothers of women with PCOS; CG♂ — male control group

Table III. *Comparison of hormonal parameters in the sisters with and without PCOS*
Tabela III. *Porównanie parametrów hormonalnych u sióstr z PCOS i sióstr bez tego zespołu*

	$S_{PCOS(-)}$ (n = 36)	$S_{PCOS(+)}$ (n = 8)	p
Testosterone [ng/mL]	0.537 ± 0.190	1.025 ± 0.170	< 0.001
SHBG [nmol/L]	45.989 ± 28.466	35.0 ± 8.538	ns
FAI	5.290 ± 3.133	11.377 ± 3.446	<0.001
Androstenedione [ng/mL]	3.414 ± 1.054	5.131 ± 1.166	< 0.001
DHEA-S [μg/dL]	236.953 ± 98.807	277.0 ± 82.604	ns
LH [mIU/mL]	6.846 ± 4.440	10.307 ± 8.531	ns
LH/FSH	1.171 ± 0.726	1.770 ± 1.256	0.07454

$S_{PCOS(+)}$ — sisters with PCOS; $S_{PCOS(-)}$ — sisters without PCOS

The hormonal parameters in sisters with and without PCOS are shown in Table III. Mean testosterone and androstenedione levels, and FAI, were significantly higher in sisters with PCOS compared with the sisters without PCOS.

The hormonal parameters in brothers with and without premature balding are summarised in Table IV. Prematurely balding brothers did not differ from the non-balding brothers in hormonal parameters.

Discussion

The initial reports on the familial occurrence of PCOS symptoms came 40 years ago. But only in the last de-

Table IV. *Comparison of hormonal parameters in the brothers with and without premature balding*
Tabela IV. *Porównanie parametrów hormonalnych u braci z przedwczesnym łysieniem i braci bez łysienia*

	$B_{PCOS(NB)}$ (n = 31)	$B_{PCOS(B)}$ (n = 11)	p
Testosterone [ng/mL]	6.105 ± 2.123	5.682 ± 0.997	ns
SHBG [nmol/L]	23.064 ± 7.938	21.764 ± 5.999	ns
FAI	99.872 ± 45.673	97.191 ± 19.910	ns
Androstenedione [ng/mL]	3.142 ± 0.940	3.079 ± 0.776	ns
DHEA-S [μg/dL]	312.742 ± 106.863	304.636 ± 85.717	ns
LH [mIU/mL]	3.009 ± 1.319	2.565 ± 0.958	ns
LH/FSH	0.923 ± 0.523	0.773 ± 0.408	ns

$B_{PCOS(B)}$ — brothers with premature balding; $B_{PCOS(NB)}$ — brothers without premature balding

cade has particular attention been paid to issues concerning a genetic background of PCOS and inheritance of this syndrome. Our study aimed to assess siblings of patients with PCOS for hormonal abnormalities typical of this syndrome. For the purposes of the study, 44 sisters and 42 brothers of women with PCOS were included.

The results of previously published studies indicate possible inheritance of hormonal disorders occurring in PCOS by first-degree relatives of women with this syndrome [7–10, 14–16]. Some of the female relatives fulfill the diagnostic criteria of PCOS [7, 8, 12]. The male phenotype that has been proposed in PCOS families includes premature balding (at an age less than 30) [13, 14]. There is evidence that prematurely balding male relatives of women with PCOS may have some typical-for-PCOS hormonal abnormalities [13, 14].

In the sisters of the PCOS patients, we observed significantly higher levels of total testosterone and DHEA-S than in the women of the control group. In eight of the 44 sisters (18.2%), a diagnosis of PCOS was made on the basis of raised concentration of testosterone, FAI and a positive interview concerning menstrual irregularities. These observations are partially consistent with the results of Legro, who recognised the syndrome in 22% of sisters of PCOS patients [8]. But that study also showed hyperandrogenaemia in some other sisters (24%), which was not observed in our study. In addition to elevated concentrations of testosterone and DHEA-S, Legro also found higher concentrations of LH in sisters of PCOS patients compared to a control group. Our study found no statistically significant differences in LH concentration and the LH/FSH ratio between the sisters and the women of the control group. Similar proportions of sisters with PCOS to that described above have been observed by Yildiz et al. (23.2% and 16% in another study) and Kahsar-Miller et al. (32%), while Azziz et al. demonstrated that as many as 40% of sisters have PCOS [7, 9, 15, 16]. Yildiz et al. [9] found higher concentrations of androstenedione in sisters of patients with PCOS than in women of a control group. An increased concentration of this androgen in sisters of PCOS patients was also reported by Govind et al. [14]. In our study, such a difference was not observed.

Analysing hormonal parameters in the groups of brothers of PCOS patients and the control men, we found that the brothers were characterised by significantly higher concentrations of DHEA-S. Significantly higher levels of DHEA-S and testosterone in brothers of PCOS women were also reported by Legro et al. and Govind et al. The former observed significantly higher concentrations of DHEA-S in brothers of patients with PCOS than age- and BMI-matched control men [10]. They emphasised that DHEA-S is the best marker of hyperandrogenism in men. The latter authors showed a greater concentration of testosterone in first-degree male relatives of patients with PCOS who were characterised by premature alopecia compared to relatives without alopecia [14]. In contrast, Yildiz et al. found no difference in the concentrations of androgens and gonadotropins between brothers of patients with PCOS and a control group of men [9]. In our study, similarly to that of Yildiz, but in contrast to other researchers [17, 18], we did not observe a higher concentration of LH in the brothers of the PCOS women; conversely, the concentration of LH as well as the LH/FSH ratio were lower in the group of brothers of women with PCOS. The discrepancy of these results merits further investigation.

In 11 of the 42 brothers (26.2%) we recognised a IV or V type of balding using the Hamilton scale. In all these brothers, premature balding occurred before the age of 30. In the control group, only three men (7.1%) had premature balding before the age of 30. In previously published studies, the percentage of prematurely balding brothers of women with PCOS has been estimated at 6.5–19.7–20% [14, 12, 19]. The most similar frequency of premature balding to our results was found

by Govind and al.: 22% [14]. However, the authors, in contrast to our observations, showed higher concentration of testosterone in the prematurely balding male relatives of PCOS women. Dušková and al., in one third of studied men with balding before the age of 30, but not relatives of women with PCOS, demonstrated hormonal abnormalities similar to these occurring in PCOS: higher FAI, higher LH/FSH ratio and lower SHBG [13]. Besides, prematurely balding men had higher values of the insulin resistance indices than the non-balding men. These results, in the opinion of the authors, might prove the existence of a male equivalent of PCOS. In our study, prematurely balding brothers did not differ from the non-balding brothers in hormonal parameters. However, we observed lower, but significant, levels of androgens in brothers with balding compared with brothers without balding. This observation may partially result from the fact that prematurely balding brothers had higher body mass, waist circumference and WHR. Other authors have found rather higher levels of androgens and FAI in prematurely balding men, including the brothers of women with PCOS [13, 14]. Lower concentrations of androgens in the prematurely balding brothers of PCOS patients compared to their non-balding contemporaries may be the consequence of lower synthesis of androgens in insulin resistance and hyperinsulinaemia states, as suggested by Baillargeon and al. [20].

On the basis of our study results, premature balding in men before the age of of 30 should not be considered as a male PCOS equivalent. Although premature balding occurred more often in brothers of women with PCOS than in men in the control group, the balding was not related to any hormonal abnormalities typical of PCOS. Similar observations have been made by other authors [10, 21], and Legro and al. demonstrated a higher frequency of balding before the age of 30 in the control group than in the brothers of women with PCOS (19% *v.* 5.5%) [10].

Conclusions

Siblings of patients with PCOS are predisposed to the occurrence of hormonal abnormalities similar to those observed in PCOS, and expressed by increased concentrations of androgens of gonadal or adrenal origin. This may indicate a genetic background of hyperandrogenaemia in PCOS, including genes involved in steroidogenesis in both gonads and adrenals.

The symptom of premature balding below the age of 30 in brothers of women with PCOS should not be considered as a male PCOS equivalent.

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