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The Influence of Polymorphic Variants of Peroxisome Proliferator-Activated Receptor Genes in the Formation of Reproductive System Disorders in Women with Hyperandrogenism

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Abstract In the study, patients were divided into two groups: the main group, which included 98 women from 18 to 35 years old with clinical and biochemical signs of hyperandrogenism and pathology of the reproductive system, and combined two groups of diseases: subgroup I consisted of 56 patients with PCOS and subgroup II included 42 women with CAH (congenital adrenal hyperplasia) and the control group included 92 apparently healthy women of identical age without clinical and biochemical signs of hyperandrogenism and a normal reproductive system. Based on the results of genetic studies, a significant association of the polymorphic marker of the PPARG gene with the risk of developing PCOS in women who carry the unfavorable Ala allele and the associated genotypes Pro/Ala and Ala/Ala (OR=4.3; 95% CI: 2.02 – 8.94) was determined. The risk of developing PCOS when carrying this allele significantly increases by more than 4 times (OR=4.3; 95% CI: 2.02–8.94). The unfavorable allele G ($\chi 2$=13.6; p=0.01) and the genotype G/G ($\chi 2$=3.4; p=0.1) of the PPARD gene polymorphism have an independent effect on the formation of PCOS; the risk of developing pathology when carrying this allele increases 5 times (OR= 5.3). Unfavorable allelic variants of the PPARA gene polymorphism significantly increase the risk of developing PCOS by 2.5 times (OR=2.5). The contribution of the studied gene polymorphisms to the increase in the risk of developing a non-classical form of congenital adrenal hyperplasia is insignificant.

Keywords Polycystic ovary syndrome, Infertility, Hyperandrogenism, Disorder of menstrual function, Genetic studies

1. Introduction

Hyperandrogenism (HA) is one of the significant causes of reproductive disorders in women, the frequency of which ranges from 4 to 18%. The frequency of infertility ranges from 46-77%, miscarriage ranges from 30-78%. [1]. Studying the causes of reproductive disorder in patients with HA is related to certain difficulties associated with the polyetiology and heterogeneity of the disease. The problem of differential diagnosis of various hyperandrogenic conditions and correction of reproductive disorder is one of the most pressing in the practice of a gynecologist. Currently, genotyping is an important diagnostic tool for identifying most diseases [2,3,5].

Polymorphisms in genes involved in the metabolic or regulatory pathways of steroid hormone synthesis, gonadotropin action, and insulin signaling pathways have been investigated as susceptibility genes for polycystic ovary syndrome (PCOS) [3,6,7,8], but there is practically no research examining studying these genes in the non-classical form of congenital adrenal hyperplasia (CAH) [4]. To gain new insight into the role that genetic variability of PPAR may play in the pathogenesis of hyperandrogenic conditions, we assessed the polymorphic loci of the genes regulating fat and carbohydrate metabolism PPARA (rs 4253778), PPARD (rs 2016520), PPARG (rs 1801282) in the formation of reproductive disorders in women with hyperandrogenism.

Purpose of the study: To study the frequency of occurrence and the role of polymorphism of the polymorphic genes PPARA (rs 4253778), PPARD (rs 2016520), PPARG (rs 1801282) in the formation of reproductive disorders in women with hyperandrogenism of ovarian and adrenal origin.

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2. Material and Methods of the Study

The design of our study was a case-control study. As a result, our patients were divided into two groups: the main group, which included 98 women from 18 to 35 years old with clinical and biochemical signs of hyperandrogenism and pathology of the reproductive system, and combined two groups of diseases: subgroup I consisted of 56 patients with

PCOS and subgroup II included 42 women with nonclassic CAH and the control group included 92 apparently healthy women.

Genotyping of the polymorphism of the polymorphic genes PPARA (rs 4253778), PPARD (rs 2016520), PPARG (rs 1801282) was carried out by PCR on programmable thermal cyclers CG-1-96 "CorbettResearch" (Australia) and 2720 "Applied Biosystems" (USA), using the test systems "MedLab" (Russia), according to the manufacturer's instructions.

3. Results and Discussion

When studying the distribution frequency of alleles and genotypes of the G/C polymorphism in the gene PPARA in the patients with PCOS and the control group, the unfavorable allele C was insignificantly more common - in 28% of cases it prevailed in the group with PCOS ($\chi2$=1.6; p=0.3; RR=1.1; 95 %CI: 0.69 - 1.71; OR=1.4; 95%CI0.83 - 2.45), compared with the control group, in which it was detected in 21%.

The genotype C/C was detected in the group with PCOS in 11% of the patients, which was insignificantly more common ($\chi2$=0.8; p=0.4; RR=1.6; 95% CI: 0.5-5.4; OR=1.7; 95% CI: 0.53 - 5.56) than in the control group, which was 7%. At the same time, the allele C in nonclassic CAH was detected insignificantly 13% less often compared to the control group, where its frequency was 21% ($\chi2$=2.5; p=0.2; RR=0.9; 95% CI: 0.64 - 1.28; OR=0.6; 95% CI: 0.27 - 1.15). The genotype C/C insignificantly predominated 6.5% in the control group; in nonclassic CAH it was 2% ($\chi2$=1.0; p=0.40; RR=0.4; 95% CI: 0.01-13.23; OR=0.3; 95%CI: 0.04 -2.75). The unfavorable allele C is significantly more common in the group of patients with PCOS and amounted to 28%, in contrast to patients with nonclassic CAH, the frequency of which was 13% ($\chi2$=6.1; p=0.03). In the presence of the mutant allele C, the risk of developing pathology increases by 2.5 times (OR=2.5; 95%CI: 1.21-5.33). The unfavorable homozygous genotype C/C was not significantly more often identified in the group of patients with PCOS in 11% of cases, in contrast to 2% of patients with nonclassic CAH ($\chi2$=2.5; p=0.2; RR=4.5; 95%CI: 2 .24 - 9.02; OR=4.9; 95% CI: 0.69 - 35.28). Differences in the frequency of the given genotype can be regarded as a statistical trend. (OR=4.9; 95% CI: 0.69 - 35.28). Thus, we were unable to establish a significant associative relationship between unfavorable genotypes of this polymorphism and the development of pathology. But a significant trend can be observed that the genotype C/C has a predisposing effect on the development of PCOS. According to the calculated odds ratio, the presence of this genotypic variant increases the risk of developing this pathology by 5 times without achieving statistical significance (OR=4.9; $\chi2$=2.5; p=0.2). For the final answer, the sample size should be increased and a larger number of patients with this form of pathology and healthy women should be included in the study.

Considering the high risk of developing metabolic disorders leading to reproductive disorders when carrying an unfavorable allelic variant of the Pro12Ala polymorphism of the gene PPARG, we analyzed the frequency of occurrence and the role of the gene in the development of reproductive system disorders in women with hyperandrogenism of ovarian and adrenal origin.

The proportion of carriers of the unfavorable Ala allele turned out to be significantly 3.6 times higher among patients with PCOS compared to the control group (19.6% versus 5.4%, respectively: $\chi2$=14.6; p=0.01). The calculated risk of developing PCOS when carrying this allele significantly increases by more than 4 times (OR=4.3; 95%CI: 2.02 – 8.94). The proportion of carriers of the unfavorable homozygous genotype Ala/Ala turned out to be insignificantly (trend) higher among patients with PCOS (5%) compared to the control group (1%). The odds ratio for detecting this genotypic variant of the gene PPARG in the subgroup of patients with PCOS turned out to be very high and amounted to -OR=5.2 with a confidence interval of 95%CI: 0.65–40.73.

The unfavorable Ala allele was found insignificantly 4% less frequently among the patients with nonclassic CAH, compared to the control group, where its frequency was 5.4% ($\chi2$=0.4; p=0.6; OR=0.6; 95% CI: 0.17 –2.38), however, the Ala/Ala genotype was not detected in these women. According to the results of genotyping of the Pro12Ala polymorphism in the gene PPARG, a significant increase in the frequency of the minor Ala allele was found to be almost 5.5 times among the patients with PCOS compared to the subgroup of patients with nonclassic CAH 19.6% versus 3.6%, respectively ($\chi2$=11.1; p =0.01; OR=6.6; 95% CI: 2.18-19.99). Carrying the unfavorable Ala allele, the associated Pro/Ala and Ala/Ala genotypes, is a risk factor for the development of this pathology (OR>1). The proportion of carriers of the unfavorable Ala allele turned out to be significantly higher among patients with PCOS compared to the control group (19.6% versus 5.4%, respectively: $\chi2$=14.6; p=0.01). The calculated risk of developing PCOS when carrying this allele significantly increases by more than 4 times (OR=4.3; 95% CI: 2.02 – 8.94). When studying the frequency of occurrence of genotypes of the Pro12Ala polymorphism of the gene PPARG, there was also a significant increase in the proportion of carriers of the unfavorable Pro/Ala genotype by 4.2 times in the subgroup of patients with PCOS compared to the control group (19.4% and 8.7%, respectively; $\chi2$=4.4; p=0.05). At the same time, the odds ratio for detecting this genotype was OR=4.2, with a confidence interval of 95% CI: 1.73-10.17. Thus, our data coincide with international data and the PPARG Pro12Ala gene polymorphism can be used as a biomarker for early diagnosis and clinical prediction of metabolic risk in PCOS.

When studying the distribution frequency of alleles of the A/G polymorphism in the gene PPARD (rs2267668), we found that the frequency of occurrence of the unfavorable allele G was not significantly higher in the group with PCOS, where it was 36%, compared to the group with nonclassic CAH, where it was found in 10% and to the control group, where it was in 17% ($\chi2$= 2.5; p=0.2; OR=0.5; 95% CI: 0.23 - 1.17).

The heterozygous genotype A/G was also significantly more often found in the group with PCOS – in 46.4%, compared to the control group, which was 25.0% ($\chi2$=7.2; p=0.01; OR=2.6; 95% CI: 1.29-5.22). It is also possible to trace a trend that the unfavorable G/G genotype has a predisposing effect on the development of PCOS (12.5% versus 4.3%, respectively; $\chi2$=3.4; p=0.1). According to the calculated odds ratio, carrying the genotypic variant G/G increased the risk of developing this form of pathology by more than 3 times (OR=3.1 with a confidence interval of 95%CI: 0.92–10.69). In contrast, the frequency of detection of the A/G genotype was statistically insignificantly lower in the group with nonclassic CAH than in the control group, amounting to 9.5% and 25.0%, respectively ($\chi2$=4.3; p=0.05; RR=0.4; 95% CI: 0.06 -2.4; OR=0.3; 95% CI: 0.11-0.94). At the same time, the homozygous G/G genotype of this locus was distributed evenly within the studied subgroups and the control group of patients (5% versus 4%, respectively). The identified differences among patients with nonclassic CAH and those in the control group are not significant and do not even allow us to identify trends in its distribution (p = 0.9). Thus, functionally unfavorable variants of the rs2267668 polymorphism of the gene PPARD have an independent effect on the pathogenesis of PCOS. Carrying the genotypic variant G/G of the A/G polymorphism gene in the gene PPARD (rs2267668) increases the risk of developing PCOS by more than 3 times (OR=3.1; 95% CI: 0.92–10.69). However, despite the significant significance of this polymorphism in the dysregulation of fat and lipid metabolism, the contribution of the studied polymorphism to the increase in the risk of developing nonclassic CAH is insignificant ($\chi2$=0.0; p=0.95; OR=1.1).

4. Conclusions

The results of a study of G/C polymorphism in the gene PPARA showed that carriers of the unfavorable allele C are significantly more common in the group of patients with PCOS and amounted to 28%, in contrast to patients with nonclassic CAH, the frequency of which was 13% ($\chi2$=6.1; p=0.03). Unfavorable allelic variants of the G/C polymorphism in the gene PPARA significantly increase the risk of developing PCOS by 2.5 times (OR=2.5; 95%CI: 1.21-5.33). The contribution of the studied gene polymorphisms to the increase in the risk of developing nonclassic CAH is insignificant.

1. A significant relationship was identified between the risk of developing PCOS and carrying the unfavorable Ala allele of the Pro12Ala polymorphism of the gene PPARG. The risk of developing the disease when carrying this allelic variant significantly increases by more than 4 times (OR=4.3; 95%CI: 2.02 – 8.94).
2. Functionally unfavorable variants of the rs2267668 polymorphism of the gene PPARD have an independent effect on the pathogenesis of PCOS. The unfavorable allele G ($\chi2$=13.6; p=0.01) and genotype G/G ($\chi2$=3.4; p=0.1) of the rs2267668 polymorphism of the gene PPARD have an independent effect on the formation of PCOS; the risk of developing pathology when carrying this allele increases 5 times (OR =5.3; 95% CI: 2.44-11.43).

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