Effect of estrogen receptor gene ESR1 polymorphism on development of premenstrual syndrome

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To identify risks of development of any disease is a priority of modern medicine. The aim of this study was to investigate the frequency of polymorphic variants of A-351G gene estrogen receptor ESR1 in patients with various forms of PMS. Molecular genetic analysis of ESR1 gene polymorphism in 50 women with PMS (25 women of them had edematous form of disease, 25 – neuropsychical, 25 – mild, 25 – severe form) was carried out. 25 women without diagnosis of PMS were examined as controls.

The study A-351G polymorphism estrogen gene ESR1 showed no statistically significant differences in the frequency of distribution of genotypes and alleles between women with PMS and without this pathology. However, the frequency of GG genotype in women with severe PMS was significantly higher in 8.0 times compared with healthy women (χ²=4.87, p=0.03) and in women with edematous form of PMS – in 7.0 times (χ²=3.72, p=0.05). Thus, a polymorphic variant of A-351G gene ESR1 estrogen can be considered as a marker of PMS. Pathological variant GG genotype was significantly associated with the presence of edematous and severe forms of the disease.

Key words: premenstrual syndrome, estrogen receptor gene ESR1, polymorphism.
MATERIAL AND METHODS

The study included 200 women with premenstrual syndrome, which formed basic group. The control group consisted of 50 healthy women without diagnosis of PMS. Verification of diagnosis and severity of disease (mild and severe) was performed according to Order of Ministry of Health of Ukraine № 676 from 31.12.2004 [5]. Diagnosis of PMS was exhibited by presence of cyclical manifestations of the disease in luteal phase of menstrual cycle on the basis of history-taking and results of patient’s self-observation diary for 2–3 menstrual cycles (R. Moos Menstrual Distress Questionnaire). Form of PMS (edematous, neuropsychical, cephalgic, crisis) was determined in accordance with the classification of V.P. Smetnik’s [6]. Clinical examination was carried out on the basis of Ivano-Frankivsk clinical maternity hospital (Ivano-Frankivsk, Ukraine).

The criteria for inclusion of patients in research were: the reproductive age (18–44 years), regular menstrual cycles, presence of PMS, written consent of the patient. Exclusion criteria: women who had at the time of the study pregnancy or lactation, disorders of menstrual cycle, focal lesions of breast, dysfunctional uterine bleeding of unknown etiology, acute inflammation of pelvic organs, tumors of uterus and ovaries of unknown etiology, endometrial hyperplasia, genital endometriosis, severe somatic pathology in the history, organic pathology of the central nervous system, mental illness, hormonal tumors, diabetes, adrenal diseases, malignant tumors in the present or in anamnensis, premenstrual dysphoric disorder, women who took psychotropic medications or hormonal therapy within the last 3 months.

The average age of women in control and basic groups was not statistically different and was respectively 28.82±0.76 and 30.13±0.36 years (p=0.08). Age of menarche corresponded in two groups – 12.94±0.13 and 12.86±0.06 years and had no differences depending on the form of PMS (p>0.05). We found

The frequency of polymorphic variants of A-351G estrogen receptor gene ESR1 among examined women

| Groups                   | n    | GG genotype | AG genotype | AA genotype |
|--------------------------|------|-------------|-------------|-------------|
| Control group            | 25   | 1           | 4.0         | 15          | 60.0        | 9            | 36.0        |
| Edematous form of PMS    | 25   | 7           | 28.0        | 9           | 36.0        | 9            | 36.0        |
| Neuropsychical form of PMS | 25   | 4           | 16.0        | 11          | 44.0        | 10           | 40.0        |
| Mild form of PMS         | 25   | 3           | 12.0        | 14          | 56.0        | 8            | 32.0        |
| Severe form of PMS       | 25   | 8           | 32.0        | 6           | 24.0        | 11           | 44.0        |
| Basic group, total       | 50   | 11          | 22.0        | 20          | 40.0        | 19           | 38.0        |

Table 1

The frequency of genotypes of estrogen receptor gene ESR1 among examined women, depending on form of PMS compared with control group

| Groups                   | n   | GG genotype | AG genotype | AA genotype |
|--------------------------|-----|-------------|-------------|-------------|
| Control group            | 25  | 4.0         | 60.0        | 36.0        |
| Edematous form of PMS    | 25  | 28.0        | 3.72        | 0.05        | 36.0        | 2.00        | 0.16        | 36.0        | 0.09        | 0.77        |
| Neuropsychical form of PMS | 25  | 16.0        | 0.89        | 0.35        | 44.0        | 0.72        | 0.39        | 40.0        | 0.00        | 1.00        |
| Mild form of PMS         | 25  | 12.0        | 0.27        | 0.60        | 56.0        | 0.00        | 1.00        | 32.0        | 0.00        | 1.00        |
| Severe form of PMS       | 25  | 32.0        | 4.87        | 0.03        | 24.0        | 5.25        | 0.01        | 44.0        | 0.08        | 0.77        |
| Basic group, total       | 50  | 22.0        | 2.79        | 0.09        | 40.0        | 1.93        | 0.16        | 38.0        | 0.01        | 0.93        |

Table 2

Note: p – probability of the difference of indicator relative to control group.
that the average age of onset of this disease was 23.79±0.29 years. 45 (90.0%) women in control group had a history of gynecological diseases, 31 (62.0%) women of them had two or more diseases. In basic group we noticed a similar trend, the figures were, respectively, 198 (99.0%) and 136 women (68.0%). A significant percentage of gynecological pathology occupied chronic inflammation of uterine appendages (68.0% and 59.0%, respectively), as well as inflammation of the lower genital tract (44.0% and 54.5%). 26.0% of women in both groups had menstrual disorders in anamnesis. Only 22 women (44.0%) in control group had a history of pregnancy, which was 1.59 times lower than in basic group (140 women – 70.0%; 44.0%) in control group had a history of pregnancy, which was 1.59 times lower than in basic group (140 women – 70.0%; χ²=4.87, p=0.03). The odds ratio of groups with edematous and severe forms of PMS compared with control group is high (OR=9.33–11.29, p=0.03–0.04), and points to a possible association of AG polymorphism in the development of the disease (Table 3).

Women with edematous form of PMS had significantly higher in 7.0 times frequency of GG genotype compared with healthy women (χ²=5.25, p=0.02, OR=0.21, 95% CI 0.06–0.71, p=0.01, table 2). In women of basic group GG genotype was determined at 5.50 times more than of control one (22.0% and 4.0%, respectively), but the differences did not reach statistical significance (χ²=2.79; p=0.09, OR=6.77, 95% CI 0.82–55.79, p=0.07). Mark OR of the distribution of GG genotype in women with PMS compared with healthy women greater than 1, namely 6.77, may indicate a possible association of AG polymorphism in the development of the disease.

Thus, GG genotype may be regarded as a marker for increased risk of PMS, namely, its severe and edematous forms.

The frequency of the homozygous genotype AG was similar in both groups, but among healthy women met at 1.50 times more than in patients with PMS and reached 60.0% and 40.0%, respectively (χ²=1.93; p=0.16, OR=0.44, 95% CI 0.17–1.18; p=0.10).

In women with edematous, neuropsychical and mild forms of disease AG genotype was predominant (table 1).

However, we found that 24.0% of women with severe PMS found significantly lower in 2.50 times frequency of AG genotype compared with healthy women (χ²=5.25, p=0.02, OR=21, 95% CI 0.06–0.71, p=0.01, table 2).

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RESULTS AND THEIR DISCUSSION

We found no statistically significant differences in the distribution of allele and genotype frequencies of A-351G polymorphic estrogen receptor gene ESR1 between women of control and basic groups (see fig. 1). The frequency of heterozygous genotype AG was similar in both groups, but among healthy women met at 1.50 times more than in patients with PMS and reached 60.0% and 40.0%, respectively (χ²=1.93; p=0.16, OR=0.44, 95% CI 0.17–1.18; p=0.10).

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Thus, GG genotype may be regarded as a marker for increased risk of PMS, namely, its severe and edematous forms.

The frequency of the homozygous AA genotype was similar in the two groups of patients (38.0% of women with PMS and 36.0% of healthy women) and did not differ significantly depending on the clinical form and course of the disease.

G allele was determined in 31 (62.0%) women with PMS and 16 (64.0%) healthy women, A allele – in 49 (98.0%) and 24 (96.0%) persons, respectively. Distribution of G allele in women with various forms of PMS was approximately the same: in patients with edematous form it was determined in 16 (64.0%) women, neuropsychical – 15 (60.0%), mild – 17 (68.8%), severe – 14 (56.0%). A allele was found in 18 (72.0%) women with edematous form of PMS, 21 (84.0%) – neuropsychical, 22 (88.0%) – mild, 17 (68.0%) – severe. Statistically significant differences between groups were not observed.

| Forms of PMS               | Mark | GG genotype | AG genotype | AA genotype |
|----------------------------|------|-------------|-------------|-------------|
| Edematous form of PMS      | OR   | 9.33        | 0.37        | 1.00        |
|                            | CI   | 1.05-82.78  | 0.12-1.18   | 0.31-3.17   |
|                            | p    | 0.04        | 0.09        | 1.00        |
| Neuropsychical form of PMS | OR   | 4.57        | 0.52        | 1.18        |
|                            | CI   | 0.47-44.17  | 0.17-1.61   | 0.38-3.72   |
|                            | p    | 0.19        | 0.26        | 0.77        |
| Mild form of PMS           | OR   | 3.27        | 0.85        | 0.84        |
|                            | CI   | 0.32-33.84  | 0.27-2.61   | 0.26-2.70   |
|                            | p    | 0.32        | 0.77        | 0.77        |
| Severe form of PMS         | OR   | 11.29       | 0.21        | 1.39        |
|                            | CI   | 1.29-98.89  | 0.06-0.71   | 0.45-4.35   |
|                            | p    | 0.03        | 0.01        | 0.56        |
| Basic group, total         | OR   | 6.77        | 0.44        | 1.09        |
|                            | CI   | 0.82-55.79  | 0.17-1.18   | 0.40-2.95   |
|                            | p    | 0.07        | 0.10        | 0.87        |

Table 3

Genotypes A-351G polymorphism of estrogen receptor gene ESR1 as risk markers of PMS
Estrogen receptor gene ESR1 polymorphism as a factor of development of PMS is studied poorly. N.V. Aganezova indicates approximately the same distribution of genotypes A/G gene ESR between women with PMS and without this pathology, which corresponds to the results of our study. The author confirms that for women with PMS and genotype GG are characterized by mood swings, as well as such phenomena as affective lability, tendency to asthenic, hypochondriacal, anancastic features [1]. Therefore, this genotype she considers as «a marker which indirectly predisposes originality emotional and personal characteristics of women with PMS» [2].

CONCLUSION

A polymorphic variant of A-351G gene estrogen receptor ESR1 can be regarded as a marker for the development of PMS. Pathological variant GG genotype was significantly associated with the presence of edematous and severe forms of the disease.

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