UDC 618.17+575.113

Role of genetic factors in the development of premenstrul syndrome

L.V. Pakharenko
SHEE «Ivano-Frankivsk National Medical University»

To identify risks of development of any disease is a priority of modern medicine. The article deals with ESR1 gene polymorphisms and its role in the development of premenstrual.
The objective: **of this study was to investigate the frequency of polymorphic variants of A-351G gene estrogen receptor ESR1 in patients with various forms of premenstrual syndrome.**
Materials and methods**. Molecular genetic analysis of ESR1 gene polymorphism was determines in 50 women with premenstrual syndrome (25 women of them had edematous form of disease, 25 – neuropsychical one; 25 suffered from mild form, 25 – severe one). 25 women without diagnosis of premenstrual syndrome were examined as controls.**
Results**. The study of A-351G polymorphism estrogen gene ESR1 demonstrated no statistically significant differences in the frequency of distribution of genotypes and alleles between women with premenstrual syndrome 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 (χ^2=4,87; p=0,03) and in women with edematous form of PMS – in 7,0 times (χ^2=3,72; p=0,05).**
Conclusion**. Thus, a polymorphic variant of A-351G estrogen receptor gene ESR1 can be regarded as a marker for the development of premenstrual syndrome. Pathological variant GG genotype is significantly associated with the presence of edematous and severe forms of the disease.**
Key words: *premenstrual syndrome, genetic factors, development.*

Premenstrual syndrome (PMS) – is a functional disorder of the central nervous system under the influence of adverse exogenous or endogenous factors on the background of the acquired or congenital liability of hypothalamic-pituitary-ovarian system [5]. Symptoms of psychological, endocrine, vegetative, metabolic nature arise in the luteal phase of menstrual cycle and significantly disturb usual life of a woman.

Hormonal aspects of PMS are convincing. One of the first theories of development of this disease is the theory of hyperestrogenemy. Estrogens exert their effects on cells by binding with α or β receptors. These receptors are encoded by genes ESR1 and ESR2. Expression of these genes is located not only female in genital tissues, but also in cells of the prostate, heart, lungs, kidneys, etc. [2]. There are only some reports about of ESR gene polymorphism in the development of gynecological pathology. This is possibly due to the relatively recent tendency of research and development of new technologies in medicine. Close relationship of A/G polymorphism of ESR1 gene with endometriosis and infertility on its background was found, but at the same time there is no association of ESR2 gene polymorphism with development of this disease [7]. In women with infertility and low response to ovarian stimulation genotype AG gene ESR1 was determined most frequently [4]. ESR1 gene polymorphism may be associated with the development of dysmenorrhea [12], migraine [9, 10], the regulation of behavior and mood of women [8, 11].

The objective: 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.

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 the 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).

Inclusion criteria: the reproductive age (18–44 years), regular menstrual cycle, presence of PMS, written consent of the patient. Exclusion criteria: pregnancy, lactation, disorders of menstrual cycle, focal lesions of breast, abnormal 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, thyroid patholigy, malignant tumors in the present or in anamnesis, 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 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 198 (99.0%) and 136 women (68.0%) respectively. A significant percentage of gynecological pathology occupied chronic inflammation of uterine appendages (68.0% and 83.5%, 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%; χ^2=10.74; p=0.001, OR=2.97, 95% CI 1,57–5,60; p<0.001). Noteworthy is the fact that women with PMS had more labors – 64.5% versus 38.0% in control group (χ^2=10.56; p=0.001, OR=2.96, 95% CI 1.56–5.62; p<0.001).

Given that the most common forms of PMS are edematous and neuropsychical ones, we performed molecular genetic analysis of ESR1 gene polymorphism in 50 women of basic group: 25 of them had edematous form of disease, 25 – neuropsychical one; 25 of them suffered from mild PMS, 25 – severe. Also 25 women of control group were examined.

A-351G polymorphism of the estrogen receptor gene ESR1 was determined in the research laboratory of Department of

The frequency of A-351G polymorphism of the estrogen receptor gene ESR1 in women with different forms of premenstrual syndrome

Groups	n	GG genotype		AG genotype		AA genotype	
		Abs.	%	Abs.	%	Abs.	%
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

Medical Genetics, Shupyk National Medical Academy of Postgraduate Education (Kyiv). Material for the study was the peripheral blood, which was took into tubes with EDTA in amount of 2.7 ml, then DNA was isolated using a commercial set "DNA-sorb-B" (Institute of Epidemiology of the Ministry of Health of Russian Federation). After the polymerase chain reaction with the reagents of the company Fermentas (Lithuania) in thermocycler «FlexCycler» (Analytik, Jena, Germany) restriction fragment length polymorphism was analyzed. The amplification products of A-351G gene ESR1 fragments were splitted using restriction endonuclease PvuII. Then, electrophoresis of resulting fragments in 2% agarose gel with the addition of ethidium bromide and visualization by computer system Vitran were performed

For statistical analysis of the results we used the criterion χ^2, odds ratio (OR), confidence interval (CI).

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. The frequency of heterozygous genotype AG was similar in both groups, but among healthy women it met in 1.50 times more often than in patients with PMS and reached 60.0% and 40.0%, respectively (table). In women with neuropsychical and mild forms of disease AG genotype was predominant. 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 (χ^2=5.25; p=0.02, OR=0.21, 95% CI 0.06–0.71; p=0.01). In women of basic group GG genotype was determined at 5.50 times more than of control one, but the differences did not reach statistical significance (χ^2=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.

Women with edematous form of PMS had significantly greater in 7.0 times frequency of GG genotype (28.0%) than in control group (χ^2=3.72, p=0.05; OR=9.33, 95% CI 1.05–82.78, p=0.04). A rate of GG genotype in women with severe PMS met more often in 8.0 times compared with healthy women, and accounted for 32.0% (χ^2=4.87, p=0.03; OR=11.29, 95% CI 1.29–-98.89, p=0.03). The odds ratio of groups with edematous and severe forms of PMS compared with control group is high, and points to the link of GG genotype with the occurrence of a certain form 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 AA genotype was similar in control and basic groups 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.

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 sees as «a marker which indirectly predisposes originality emotional and personal characteristics of women with PMS» [3].

CONCLUSION

A polymorphic variant of A-351G estrogen receptor gene 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.

Роль генетических факторов в развитии предменструального синдрома

Л.В. Пахаренко

Определение рисков развития болезни является приоритетным направлением современной медицины. Статья посвящена изучению роли полиморфизма гена ESR1 в развитии предменструального синдрома.

Цель исследования: изучение частоты полиморфных вариантов A-351G гена–рецептора эстрогена ESR1 у больных с различными формами предменструального синдрома.

Материалы и методы. Проведен молекулярно-генетический анализ полиморфизма гена ESR1 у 50 женщин с предменструальным синдромом, из них у 25 женщин диагностировано отечную форму заболевания, у 25 – нейропсихическую, а также 25 женщин имели легкую форму патологии, 25 – тяжелую. Также было обследовано 25 женщин без данного диагноза.

Результаты. В результате исследования A-351G полиморфного локуса гена–рецептора эстрогена ESR1 не было выявлено статистически значимых различий в распределении частот генотипов и аллелей между женщинами с предменструальным синдромом и без этой патологии. Однако частота генотипа GG у женщин с тяжелой формой заболевания была достоверно выше – в 8,0 раза по сравнению со здоровыми женщинами (χ^2=4,87; p=0,03), а у женщин с отечной формой – в 7,0 раза (χ^2=3,72; p=0,05).

Заключение. Таким образом, полиморфный вариант A-351G гена–рецептора эстрогена ESR1 можно рассматривать как маркер развития предменструального синдрома. Патологический вариант GG-генотипа достоверно ассоциируется с наличием отечной и тяжелой форм заболевания.

Ключевые слова: *предменструальный синдром, генетические факторы, развитие.*

Роль генетичних факторів у розвитку передменструального синдрому

Л.В. Пахаренко

Визначення ризиків розвитку хвороби є пріоритетним напрямком сучасної медицини. Стаття присвячена вивченню ролі поліморфізму гена ESR1 у розвитку передменструального синдрому.

Мета дослідження: вивчення частоти поліморфних варіантів A-351G гена–рецептора естрогену ESR1 у хворих з різними формами передменструального синдрому.

Матеріали та методи. Проведено молекулярно-генетичний аналіз поліморфізму гена ESR1 у 50 жінок з передменструальним синдромом, з них у 25 жінок діагностовано набрякову форму захворювання, у 25 – нейропсихічну, а також 25 жінок мали легку форму патології, 25 – тяжку. Також було обстежено 25 жінок без цього діагнозу.

Результати. У результаті дослідження A-351G поліморфного локусу гена–рецептора естрогену ESR1 не було виявлено статистично значущих відмінностей у розподілі частот генотипів і алелів між жінками з передменструальним синдромом і без цієї патології. Однак частота генотипу GG у жінок з тяжкою формою захворювання була достовірно вищою – у 8,0 разу порівняно зі здоровими жінками (χ^2=4,87; p=0,03), а у жінок з набряковою формою – у 7,0 разу (χ^2=3,72; p=0,05).

Заключення. Отже, поліморфний варіант A-351G гена–рецептора естрогену ESR1 можна розглядати як маркер розвитку передменструального синдрому. Патологічний варіант GG-генотипу достовірно асоціюється з наявністю набрякової і тяжкої форм захворювання.

Ключові слова: *передменструальний синдром, генетичні фактори, розвиток.*

Сведения об авторе

Пахаренко Людмила Владимировна – Кафедра акушерства и гинекологии Ивано-Франковского национального медицинского университета, 76018, г. Ивано-Франковск, ул. Галицкая, 2; тел.: (097) 430-69-21. *E-mail: ludapak@ukr.net*

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Статья поступила в редакцию 27.06.2018