ASSESSMENT OF ESTROGEN RECEPTOR GENE POLYMORPHISM (T-397C VARIANT) IN PATIENTS WITH PREMENSTRUAL SYNDROME

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ABSTRACT
The aim: of the study is to determine the frequency of polymorphism of estrogen receptor gene ESR1 (T-397C variant) in patients with premenstrual syndrome.

Materials and methods: 50 women with diagnosis of premenstrual syndrome (the basic group) and 25 persons without it (the control group) were examined. Polymerase chain reaction was used to study T-397C polymorphism of estrogen receptor gene ESR1.

Results: There was no significant difference in allele and genotype rates of ESR1 gene between persons with premenstrual syndrome and controls. TT genotype was determined in 24.0 % women in the control group and 24 % of patients in basic group (OR=1.00, 95 % CI=0.32-3.08, p=1.00), TC genotype – in 52.0 % and 46.0 % of individuals respectively (OR=0.79, 95 % CI=0.30-2.06, p=0.62), CC genotype – 24.0 % and 30.0 % of women respectively (OR=1.36, 95 % CI=0.45-4.07, p=0.59). Also, the frequency of T allele and C allele was similar in individuals with pathology and healthy women. There was no significant difference in allele and genotype rates of T-397C variant of ESR1 gene between patients with mild and severe forms of premenstrual syndrome and controls.

Conclusions: There is no association of T-397C polymorphic variant of estrogen receptor gene ESR1 with the development of premenstrual syndrome.

KEY WORDS: premenstrual syndrome, estrogen receptor, polymorphism

INTRODUCTION
Premenstrual syndrome (PMS) is a common neuroendocrine syndrome in gynecology. 95 % of women of reproductive age suffer from this pathology, these data differ and depend on the population, ethnic group, age, used diagnostic criteria [1]. The complex of numerous physical and psychological symptoms which occur in the second phase of the menstrual cycle and lead to daily functional impairment composes PMS. Stress load, poor physical activity, smoking, alcohol contribute to the forming of PMS [2]. The decline of quality of life – decreased daily and professional activities are usually observed in women with this disease [3]. Thus, PMS can be considered as the biopsychological pathology [4].

Different pathogenetic mechanisms are described to explain all clinical manifestations of PMS. The changes of estrogens and progesterone (its metabolites) levels during the menstrual cycle often lead to clinical signs of the syndrome. Besides this, these hormones considered to be as neuromediators and significantly affect mood changes [5] that can cause psychological manifestations of the pathology. In addition, the role of serotoninergetic regulation, renin-angiotensin system are important in the development of PMS. Genetic aspects of PMS development are less studied. Certainly, family history has the important meaning. The significance of gene polymorphism is not established well. Nowadays the role of serotonin transporter gene polymorphism in the genesis of premenstrual dysphoric disorder was demonstrated [6].

THE AIM
The aim of the study is to determine the frequency of T-397C polymorphism of estrogen receptor gene ESR1 in patients with PMS.

MATERIALS AND METHODS
The study included 50 women with the diagnosis of PMS who formed the basic group, 25 of them had mild form of PMS and 25 – severe one. 25 women without this pathology were controls. The research was carried out in Ivano-Frankivsk City Clinical Perinatal Centre (Ukraine). Diagnosis of PMS was exhibited by the presence of cyclical manifestations of the disease in the luteal phase of menstrual cycle on the basis of history-taking and the results of patient’s self-observation diary for 2-3 menstrual cycles (R. Moos Menstrual Distress Questionnaire). Mild PMS considered as the presence of 3-4 symptoms in 2-10 days before menstruation with significant severity 1-2 of them, severe form – the existence of 5-12 symptoms in 3-14 days before menstruation, 3-4 of them are most pronounced [7].
RESULTS

The average age of the persons in the control group was 27.16±1.09 years, the basic one – 29.42±0.84 years. Menarche started approximately in equal age of women in both groups – 13.04±0.20 12.94±0.12 years respectively. The rate of gynecological pathology was also high in two groups – 13.04±0.20 12.94±0.12 years respectively. The equal distribution of CC and TT genotypes and 24.0 % respectively). There was no significant difference in the rate of carriers of T and C alleles between persons with pathology (70.0 % and 76.0 % respectively) and without it (76.0 % and 76.0 % respectively). We did not find also significant difference in the frequency of genotypes and alleles between patients with mild and severe forms of the disease. The statistical results of data did not demonstrate the increased risk of T-397C polymorphic variant of ESR1 gene in the development of PMS (table 2).

DISCUSSION

One of the main pathogenetic mechanisms of PMS development is connected with changes of estrogens and progesterone levels during the menstrual cycle. Estrogens act through the α or β receptors which are genetically encoded by estrogen receptor genes ESR1 and ESR2. The research data about the study of the polymorphism of ESR gene demonstrated its role in the genesis of different pathological diseases. There are reports about its significance as the risk factor in the forming of cancer conditions – cancer of breast [8], endometrium [9], prostate [10], hepatocellular carcinoma [11], etc. However, the meta-analysis in EMBASE, PubMed, CNKI, and
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WANFANG systems, in which the literature data were collected till 2018, suggest that ESR1PvuII (rs2234693 T>C) polymorphism may only have little impact on cancer susceptibility [12]. Tang L. et al. studied that persons who have ESR1 PvuII T allele are in the risk group of hip fracture, while the XbaI polymorphism is not associated with it [13]. Knee osteoarthritis [14], osteoporosis [15] are connected with ESR1 gene polymorphism. The carriers of TC or CC and rs9340799-AG or GG genotype have the highest knee osteoarthritis risk, compared to individuals with rs2228480-TT and rs9340799-AA genotype [16].

PvulII and Xbal polymorphisms are associated with premature ovarian rupture [17], while other researches demonstrated opposite results [18]. The risk of infertility can be related to XbaI and PvuII polymorphisms of ESRa in Pakistan population in persons with AG genotype and TC genotype [19]. GG genotype of XbaI polymorphism decrease the risk of preeclampsia, while homozygous T-A haplotype carriers of ESR1 PvuII and XbaI polymorphisms have increased risk [20]. Unexplained spontaneous abortions can be connected with ESR1 polymorphism [21]. There was no the statistically difference in the frequency distribution of the XbaI and of the PvuII genotypes and alleles between the persons with of central precocious puberty and controls. [22].

Also, the meta-analysis reported that PvuII (C>T) polymorphism was not related to the susceptibility to endometriosis except for a slight association of stage I–III endometriosis under recessive model. This meta-analysis indicated that the PvuII and XbaI polymorphisms were not associated with the risk of endometriosis [23]. Results of meta-analysis which studied the relation between ESR1 gene polymorphism (-351A/G and -397T/C variants) demonstrated the increased risk of severe preeclampsia in the carriers of GG genotype (XbaI -351A/G polymorphism) and no association of the ESR1 gene PvuII -397T/C and XbaI -351A/G polymorphisms with severe and mild preeclampsia [24].

Researches about ESR1 polymorphism as the risk factor of PMS are limited. They mostly are connected with the study of A-351G polymorphic variant. The equal frequency of A/G genotypes between women with and without PMS was found [25, 26]. Individuals with GG genotype have affective emotional features [25].

CONCLUSIONS

The study of rate of T-397C variants of estrogen receptor gene ESR1 in patients with PMS was first conducted. There is no association of T-397C polymorphic variant of estrogen receptor gene ESR1 with PMS.

Table I. The frequency of genotypes and alleles of T-397C variant of ESR1 gene in women with premenstrual syndrome.

<table>
<thead>
<tr>
<th>Genotype / allele</th>
<th>Control group, n=25</th>
<th>Mild PMS, n=25</th>
<th>Severe PMS, n=25</th>
<th>PMS, total, n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT genotype</td>
<td>6 (24.0)</td>
<td>4 (16.0)</td>
<td>8 (32.0)</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>TC genotype</td>
<td>13 (52.0)</td>
<td>15 (60.0)</td>
<td>8 (32.0)</td>
<td>23 (46.0)</td>
</tr>
<tr>
<td>CC genotype</td>
<td>6 (24.0)</td>
<td>6 (24.0)</td>
<td>9 (36.0)</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>T allele</td>
<td>19 (76.0)</td>
<td>19 (76.0)</td>
<td>16 (64.0)</td>
<td>35 (70.0)</td>
</tr>
<tr>
<td>C allele</td>
<td>19 (76.0)</td>
<td>21 (84.0)</td>
<td>17 (68.0)</td>
<td>38 (76.0)</td>
</tr>
</tbody>
</table>

Table II. Genotypes and alleles of T-397C variant of ESR1 gene as risk factors of premenstrual syndrome.

<table>
<thead>
<tr>
<th>Genotype/allele</th>
<th>Indices</th>
<th>OR</th>
<th>Mild PMS, n=25</th>
<th>Severe PMS, n=25</th>
<th>PMS, total, n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT genotype</td>
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<td></td>
<td>0.60</td>
<td>1.49</td>
<td>1.00</td>
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<tr>
<td></td>
<td>CI</td>
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<td>0.43-5.17</td>
<td>0.32-3.08</td>
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<tr>
<td></td>
<td>p</td>
<td>0.48</td>
<td>0.53</td>
<td>1.00</td>
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</tr>
<tr>
<td>TC genotype</td>
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<td></td>
<td>1.38</td>
<td>0.43</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>0.45-4.25</td>
<td>0.14-1.37</td>
<td>0.30-2.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.57</td>
<td>0.16</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>CC genotype</td>
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<td></td>
<td>1.00</td>
<td>1.78</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>0.27-3.67</td>
<td>0.52-6.09</td>
<td>0.45-4.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>1.00</td>
<td>0.36</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>T allele</td>
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<td></td>
<td>1.00</td>
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<td>0.74</td>
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<tr>
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<td>0.25-2.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>1.00</td>
<td>0.36</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>C allele</td>
<td></td>
<td></td>
<td>1.66</td>
<td>0.67</td>
<td>1.00</td>
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<tr>
<td></td>
<td>CI</td>
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<td>0.19-2.33</td>
<td>0.32-3.08</td>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>0.48</td>
<td>0.53</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


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Conflicts of interest:
The Authors declare no conflict of interest.