American Journal of Medicine and Medical Sciences 2025, 15(5): 1593-1596
DOI: 10.5923/j.ajmms.20251505.62

To Study the Role of Genetic Factors in the Development of Preeclampsia

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Abstract A retrospective case–control study was conducted: 55 pregnant women with preeclampsia (main group) and 30 patients with uncomplicated pregnancy (control group). In the main group, two subgroups were considered – early and late preeclampsia. Polymorphism of the I/D gene of the angiotensin converting enzyme ACE is associated with the risk of developing preeclampsia. It can be said that ACE gene polymorphism is a genetic predictor of the development of early and severe preeclampsia.

Keywords Early and late preeclampsia, Polymorphism of the angiotensin converting enzyme ACE I/D gene

1. Introduction

Preeclampsia is a complex medical condition that can occur in the second half of pregnancy, after the 20th week. It is characterized by high blood pressure, protein in the urine, and symptoms of organ failure. This condition can lead to high rates of perinatal and maternal mortality and morbidity.

Thus, according to current WHO data, pre-eclampsia complicates 10% of pregnancies and is the leading cause of maternal and perinatal morbidity and mortality worldwide. Every year, approximately 50,000 women die from severe pre-eclampsia, eclampsia, or hypertensive disorders worldwide. Extensive epidemiological studies have shown that heredity plays a role in the development of pre-eclampsia. The polymorphism of genes in the renin-angiotensin-aldosterone system, in particular the DD I genotype and D polymorphism of the ACE (angiotensin-converting enzyme) gene, is associated with an increased risk of pre-eclampsia and its clinical features, as well as adverse effects on the fetus and newborn. However, there is some debate about whether there are any differences in the frequency of polymorphisms in the ACE gene between pregnant women with hypertension and those with a normal pregnancy. This depends on the specific analytical model of inheritance used and the population being studied.

Impaired expression of the alpha-adducin gene (ADD1) in placental tissue at the end of the first trimester is linked to the risk of preeclampsia. However, the G460W polymorphism of the ADD1 gene does not always cause a rise in blood pressure during pregnancy. Instead, it is associated with an increase in sodium reabsorption in the kidneys, which can lead to high blood pressure. However, it is still unclear whether polymorphic variants of the ACE and ADD1 genes are linked to the development of pre-eclampsia, and how these genetic markers influence the features of phenotypes that are pathogenetically associated with high blood pressure.

The purpose of the study to investigate the association between the G460W polymorphic locus of the ADD1 gene and the I/D ACE gene in patients with preeclampsia, and to determine the effect of these genetic markers on the development of phenotypic features in pregnant women experiencing this pregnancy complication.

Received: Mar. 6, 2025; Accepted: Apr. 16, 2025; Published: May 30, 2025
Published online at http://journal.sapub.org/ajmms

2. Materials and Methods

A retrospective case–control study was conducted: 55 pregnant women with preeclampsia (the main group) and 30 patients with uncomplicated pregnancy (the control group). In the main group, two subgroups were considered – early and late preeclampsia. Daily blood pressure monitoring was performed using the MDP-HC-02 device. The average daily systolic blood pressure (SADsut) and average daily diastolic blood pressure (DADsut) were analyzed. The polymerase chain reaction method with real-time hybridization-fluorescence detection was used to type the G460W single nucleotide polymorphism of the ADD1 gene (rs4961). The ABI Prism 7500 system was used as a detecting amplifier. The typing of the I/D polymorphism of the Alu repeat in the 16-mintron (rs4340) of the ACE gene was performed by analyzing the polymorphism of the lengths of amplification fragments ("Amplicite-ACE") with detection in an agarose gel. ACE activity and plasma aldosterone concentration were determined by enzyme immunoassay, and plasma renin activity (by increasing angiotensin I levels) by radioimmune method. The daily urinary sodium excretion was studied

using ion-selective potentiometry on an EasyLyte analyzer. The distribution of genotypes was checked for compliance with the Hardy—Weinberg equilibrium using the $\chi 2$ criterion. Differences in the frequency of alleles and genotypes between the groups were assessed using the $\chi 2$ criterion with a Yates correction for continuity. To assess the association of genotypes and alleles with preeclampsia, odds ratios (OR) with a 95% confidence interval (CI) were calculated. The normality of the distribution of quantitative features was assessed using the Shapiro—Wilk criterion. The Student, Mann-Whitney, and Kraskel-Wallis criteria were used to compare independent samples. The significance of the differences was established at $p<0.05$.

3. Results and Discussion

The analysis of clinical parameters in the patients of the examined groups allowed us to establish that the average age of pregnant women in the control and main groups was 26.7±4.2 and 29.3± 6.7 years, respectively (p=0.5). Body mass index (BMI) in the pre-pregnancy period in pregnant women of the main group tended to increase (24.4±0.5 kg/m2 compared with 23.1±2.6 kg/m2 in the control group; p=0.12), as well as BMI before childbirth (30.2±3.1 kg/m2 in the main group and 27.5±2.7 kg/m2 in the control group; p=0.09), but did not significantly differ between the groups, despite the fact that overweight is classified as a strict risk factor for preeclampsia [2]. The gestation period at the time of delivery in the main group was shorter (34.2±3.8 weeks versus 39.4±1.2 weeks during the physiological course of pregnancy; p=0.03), which was associated with the need for early delivery with the progression of preeclampsia in some patients. At the same time, delayed fetal development and prematurity led to a lower body weight of newborns in the main group of patients (2720.3±460.7 g in the main group and 3640.4±370.3 g in the control group; p=0.002). The frequency distribution of the genotypes and alleles of the polymorphic loci I/D of the ACE gene and G460W of the ADD1 gene corresponded to that expected at the Hardy—Weinberg equilibrium for the main and control groups. The association analysis revealed that ACE I/D polymorphism is associated with the development of preeclampsia. Thus, the heterozygous genotype ID and the D allele are genetic predisposition factors for this pregnancy complication, increasing the risk of its development by 1.96 and 1.45 times, respectively. In turn, allele I has a protective effect on the development of preeclampsia (OR=0.68). However, most populations are characterized by an association of the development of preeclampsia with the DD genotype of the ACE gene [10-11], which allows us to consider the frequency distribution of genotypes and alleles of the ACE I/D polymorphism as a distinctive feature of the examined sample of women with preeclampsia. The differences in the distribution of the molecular variants of the G460W polymorphism of the ADD1 gene in both groups of pregnant women were insignificant and insignificant. In the analyzed samples of pregnant women, the homozygous genotype for the mutant allele of the polymorphic G460W locus of the ADD1 gene was not noted, which is probably a characteristic feature of the population of women living in Uzbekistan and the Tashkent region, in particular. A comparative analysis of the frequencies of combinations of genotypes of polymorphisms I/D of the ACE gene and G460W of the ADD1 gene in the main and control groups of women indicates a significant shift in the risk of developing preeclampsia towards its increase compared with the data of the monolocus analysis. Thus, carrying a pair of genotypes I/D ACE (DD) + G460W ADD1 (GW) increases the risk of preeclampsia by 3.11 times (OR=3.11; 95% CI 1.68—6.76; p=0.015), and pairs I/D ACE (ID)+G460W ADD1 (GW) by 2.25 times OR=2.25; 95% CI 1.29—4.98; p=0.024). Taking into account the association of dilocus combinations of genotypes I/D of the ACE gene and G460W of the ADD1 gene with the development of preeclampsia in the subgroups of these genetic markers, phenotypic criteria pathogenetically associated with increased blood pressure were studied. Plasma renin activity in the total sample of patients in the main group was lower (Iu 1.6 ng/ml/h, interquartile range 0.9—2.1 ng/ml/h) than in pregnant women in the control group (Iu 3.6 ng/ml/h, interquartile range 1.9—4.4 ng/ml/h; z=2.12; p=0.034). Despite the fact that plasma renin activity decreases in preeclampsia, Y. Kim et al. [8] note an increase in the expression of its gene in placental tissue with reciprocal inhibition of the activity of the circulating RAAS. In addition, preeclampsia increases tissue sensitivity to the effects of angiotensin II, which, along with a decrease in renin activity, supports a decrease in blood flow velocity in the uterine arteries [7]. However, the level of plasma renin activity in pregnant women did not significantly differ between the subgroups of both the main and control groups with different genotypes of the G460W polymorphic loci of the ADD1 gene and the I/D ACE gene. Plasma ACE activity in patients with preeclampsia tended to increase (Iu 39.6 u/l, interquartile range 20.1 – 61.2 u/l) compared with that in pregnant women with a physiological course of gestation (Iu 34.2 u/l, interquartile range 19.2 – 47.4 u/l; z=1.69; p=0.09) without statistical significance of the differences. At the same time, the level of placental ACE in preeclampsia increased significantly, which is directly related to the concentration of angiotensin II, the most important inducer of systemic blood pressure elevation and endothelial dysfunction [2,3]. However, in the subgroups of dilocus combinations of ADD1 and ACE genes, significant differences in ACE activity were obtained, which was significantly higher in patients with arterial hypertension with DD+ID-GW genotypes than in the similar subgroup of the control group (z=2.18; p=0.029). In addition, patients with preeclampsia in both subgroups with DD+ID genotypes of the ACE gene had higher ACE activity than in the subgroups with genotype II (z=1.97; p=0.048 and z=2.29; p=0.022). A decrease in ACE activity in a pregnant woman with genotype II of the ACE gene may be due to the fact that the structure of allele I contains a sequence of a gene region with reduced functional activity and suppressing the promoter

activity of the gene [8]. Probably due to the same circumstance, pregnant women in the control group with DD+ID genotypes also showed greater ACE activity than in the subgroups with genotype II of the ACE gene (z=2.06; p=0.039 and z=1.99; p=0.046). It is noteworthy that the genotypes of the G460W locus of the ADD1 gene had no effect on ACE activity. The concentration of aldosterone in all patients of the main group tended to decrease (Iu 377.2 pg/ml, interquartile range 78.6 – 412.4 pg/ml) compared with the aldesterone levels in pregnant women of the control group (Iu 445.2 pg/ml, interquartile range 191.4 – 502.9 pg/ml), i.e. the differences did not reach the level of statistical significance (z=1.59; p=0.11). However, in carriers of the dilocus combination of genotypes II-GG with preeclampsia, the concentration of aldosterone in the main group was significantly lower than in the similar subgroup of the control group (z=2.01; p=0.044). This is probably influenced by a decrease in ACE activity and increased sodium reabsorption, although the concentration of aldosterone largely depends on the sensitivity of the adrenal glands to angiotensin II stimulation, which increases with preeclampsia [2]. It was found that the level of CDAD was associated with the genotypes of the G460W loci of the ADD1 gene and the I/D ACE gene only in pregnant women with preeclampsia, and exclusively with the dilocus combination of genotypes (DD+ID-GW) of the studied genetic markers. In this regard, it is known that ACE activity is associated with an increase in the concentration of angiotensin II, which is the main mechanism for increasing blood pressure under the influence of ACE gene polymorphism [4,7]. It is believed that pregnant women with preeclampsia have a decrease in urinary sodium excretion and retention of this cation in the body [1]. However, according to our data, the level of daily sodium excretion in the total sample of pregnant women in the main group (Iu 142.5 mmol/day, interquartile range 129.4 – 156.9 mmol/day) did not significantly differ from that in the control (Iu 156.2 mmol/day, interquartile range 141.3 -167.6 mmol/day; z=1.69; p=0.09). At the same time, sodium excretion in patients with preeclampsia was associated with the W allele of the G460W polymorphism of the ADD1 gene. Thus, in the subgroups of carriers of this genetic marker, the quantitative trait of this phenotype showed a significant decrease compared with that in the control group. It can be assumed that in this way the ability of the mutant allele of the ADD1 gene to influence an increase in sodium reabsorption in the kidneys is manifested [9]. At the same time, an increase in circulating blood volume with increased sodium reabsorption is characteristic of the mutant allele of the ADD1 gene [5,6].

4. Conclusions

The probability of developing preeclampsia increases significantly when polymorphic variants of the DD and ID ACE gene are combined with the GW genotype of the polymorphic G460W locus of the ADD1 gene. A statistically significant association of the heterozygous genotype ID polymorphism of the ACE gene with preeclampsia has been established in the Uzbek population of women living in Tashkent and the Tashkent region. The DD and ID I/D genotypes of the ACE gene polymorphism are associated with increased ACE activity in both pregnant women with preeclampsia and healthy women, however, with the development of this pregnancy complication, patients with a deletion in the specified polymorphic variant of the ACE gene are characterized by higher ACE activity than women in the control group with the DD genotype. The study of polymorphic loci of ACE and ADD1 genes makes it possible to use these genetic markers as criteria for assessing the individual prognosis of the development and course of preeclampsia.

The highest levels of CDAD in patients with arterial hypertension are determined by a dilocular combination of the risk of developing preeclampsia, including the DD and ID genotypes of the ACE gene, as well as the GW genotype of the G460W polymorphism of the ADD1 gene.

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