

Frequency of G2677T/A and C3435T polymorphisms of MDR1 gene in preeclamptic women

Częstość występowania polimorfizmów G2677T/A oraz C3435T genu MDR1 u kobiet ze stanem przedrzucawkowym

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Abstract

Objective: Preeclampsia (PE) belongs to main causes of mortality rates of mothers, fetuses and new born children. Polymorphism of MDR1 gene is connected with reduction of P-glycoprotein expression in placenta and increased fetal exposure to xenobiotics. The aim of the study was to determine the frequency of C3435T and G2677T/A polymorphisms of MDR1 gene in pregnant women with preeclampsia.

Materials and methods: The study consisted of 180 Polish women including 60 women with PE and 120 healthy pregnant women. Determination of C3435T and G2677T/A polymorphisms of MDR1 gene was performed using PCR-RFLP method.

Results: No significant association between genotypes of the examined polymorphisms and the clinical parameters of pregnant women with PE was observed. However the interesting tendency to higher prevalence of mutated 2677A allele of G2677T/A MDR1 polymorphism in PE group has been shown (2,50 vs. 0,83% in controls, OR=3,05, ns).

Conclusions: The results of this study suggest no significant effect of examined C3435T and G2677T/A MDR1 polymorphisms in PE pathogenesis. However given the noteworthy results related to mutated 2677A allele of G2677T/A MDR1 polymorphism in preeclamptic women further studies seem to be needed. Nevertheless, the frequency of investigated polymorphisms was consistent with the distribution in other Caucasian populations.

Key words: **preeclampsia / P-glycoprotein / MDR1 gene / genetic polymorphism /**

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Streszczenie

Cel pracy: Stan przedrzucawkowy (PE – preeclampsia) należy do głównych przyczyn śmiertelności matek, płodów i noworodków na świecie. Polimorfizm genu oporności wielolekowej (MDR1 – multidrug resistance gene) jest związana ze zmniejszeniem ekspresji P-glikoproteiny w łożysku i w efekcie zwiększeniem narażenia płodu na działanie ksenobiotyków. Celem badania było określenie częstości występowania polimorfizmów C3435T oraz G2677T/A genu MDR1 u kobiet ciężarnych ze stanem przedrzucawkowym.

Materiały i metody: Analizie została poddana grupa 180 kobiet populacji polskiej, wśród nich wyróżniono 60 kobiet z PE oraz 120 zdrowych kobiet ciężarnych. Oznaczanie polimorfizmów C3435T i G2677T/A genu MDR1 przeprowadzono za pomocą techniki PCR-RFLP.

Wyniki: Nie wykazano istotnej statystycznie zależności między genotypami analizowanych polimorfizmów a parametrami klinicznymi i biochemicznymi ciężarnych z PE. W badaniu zaobserwowano jednak interesującą tendencję do większej częstości występowania zmutowanego allele 2677A polimorfizmu G2677T/A MDR1 w grupie z PE (2,50 vs. 0,83% w grupie kontrolnej, OR=3,05, ns).

Wnioski: Wyniki badania sugerują brak znaczącego wpływu badanych polimorfizmów C3435T i G2677T/A genu MDR1 na patogenezę stanu przedrzucawkowego. Jednak z uwagi na interesujące wyniki dotyczące zmutowanego allele 2677A polimorfizmu G2677T/A MDR1 u kobiet z PE istnieje potrzeba przeprowadzenia dalszych badań. Obserwowana częstość analizowanych polimorfizmów była zgodna z rozkładem w innych populacjach rasy kaukaskiej.

Słowa kluczowe: stan przedrzucawkowy / glikoproteina P / gen MDR1 /
polimorfizm genetyczny /

Introduction

The studies indicate a multifactorial background of preeclampsia (PE) however its etiology has not been fully elucidated [1, 2]. There are many studies searching for genes primarily responsible for PE development. As candidate genes that could be important in PE etiology and predispose to its development are: endothelin 1, endothelial nitric oxide synthase and genes encoding coagulation factor II, V and VII [3]. Considerations relating to the significance of genetic polymorphisms in PE development try to establish a link between selected genetic variants of multi drug resistance (MDR1) gene and the occurrence of preeclampsia. It can also assume that certain MDR1 polymorphisms affect the effectiveness of therapy in women with preeclampsia [1, 4].

P-glycoprotein (P-gp) encoded by MDR1 gene is a protein belonging to the superfamily of the ATP-binding cassette (ABC) transporters which create the blood-brain barrier and placental barrier [5]. This protein has a protective function in human organism because participates in the secretion and elimination from the body of metabolites, toxins and many drugs. Moreover, P-glycoprotein can regulate the absorption of xenobiotics including drugs from the gastrointestinal tract, thus this protein may influence the effects of treatment of many diseases [5, 6].

The high expression of MDR1 is observed among organs performing the secretory functions: liver, pancreas, kidney, small intestine and colon. Significant amounts of P-glycoprotein are also present in the endothelium, brain, testes, ovaries and placental syncytiotrophoblast cells [5]. Location of P-glycoprotein suggests that its physiological role is to protect tissues against xenobiotics [7]. In the placenta, P-glycoprotein expression is highest in early pregnancy while the protective role of this protein decreases with the pregnancy progresses [8, 9].

The presence of C3435T (exon 26) and G2677T/A (exon 21) polymorphisms of MDR1 gene is connected with the reduction of P-glycoprotein expression in placenta and consequently an increase of fetal exposure to xenobiotics [10, 11].

Aim of study

To determine the possible significance of genetic variants associated with C3435T and G2677T/A polymorphisms of MDR1 gene in the etiology of preeclampsia.

Materials and Methods

The group of 180 pregnant women from the region of Wielkopolska (Poland) were analysed (60 preeclamptic and 120 healthy pregnant women). The women were enrolled at Division of Perinatology and Women's Diseases of Poznan University of Medical Sciences. The study was approved by Local Bioethical Committee of Poznan University of Medical Sciences.

The average age of PE group was 29,45±5,12 years and mean week of gestation 33,57±3,82. Preeclampsia was recognised according to criteria cited by ACOG 2001 [12]. The mean systolic and diastolic blood pressure was 179,08±16,63 and 108,33±11,85 mmHg, respectively. The women who have demonstrated chronic hypertension, obesity, diabetes, thrombotic complications, kidney and cardiovascular diseases were excluded from the study. In all patients several parameters such as body mass before and in pregnancy, height, number of pregnancies were analysed. In addition, the urine samples of preeclamptic women were analyzed to detect proteinuria (presence of protein ≥75 mg/dL in urine sample was confirmed as diagnostic).

In control group the average age was 28,74±4,75 years and mean week of gestation 39,08±1,25. The mean systolic and diastolic blood pressure were 108,50±11,59 and 67,63±9,12 mmHg, respectively.

Genetic testing was performed at Laboratory of Experimental Pharmacogenetics, Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences. The C3435T and G2677T/A polymorphisms of MDR1 gene were determined using polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) methods. The primers (Tib MolBiol, Poland) used in PCR reaction, length of amplified products and conditions of PCR reaction were applied as previously described [14].

PCR/RFLP results were analyzed on agarose gels by visualization in the UV light using documentation system (KS 4000/Image PC, Syngen Biotech Molecular Biology Instruments).

The statistical significance of difference between control and experimental groups was assessed by SPSS 17.0 software using one-way ANOVA test (SPSS Inc.). The values of $p < 0.05$ were considered as statistical significant difference.

Results

The values of clinical and physical parameters of pregnant women were compared between the preeclamptic women and controls. The analysis of variance (ANOVA) showed a

statistically significant difference in the values of systolic and diastolic blood pressure ($p < 0.0001$) and body mass before and during pregnancy ($p < 0.026$ and $p < 0.009$) between both groups. There was also a statistically significant difference between these groups for the week of completion of pregnancy ($p < 0.0001$).

In PE the higher frequency of homozygous recessive 3435TT compared with the control group (20 vs. 14.17%, OR=1.51, ns) has been observed. Moreover, in the studied PE group, the mutated 3435T allele was noted slightly more frequent (45.00 vs. 41.67% in controls, OR=1.14, ns) (Table I).

In case of G2677T/A polymorphism the 2677TT genotype was present more frequently in the study group compared to the controls (11.67 vs. 7.5%, OR=1.62, ns). In the women with PE, the frequency of 2677GA genotype was 3.32% while in the control group the presence of this genotype was not observed. The most interesting observation was connected with mutated 2677A allele that was found more frequently in preeclamptic women (2.50 vs. 0.83% in controls, OR=3.05, ns). (Table I).

Any significant association between genotypes of studied polymorphisms and the clinical and biochemical parameters of preeclamptic women was observed. (Table II, III).

Table I. Frequency of genotypes of C3435T and G2677T/A MDR1 polymorphisms in PE and control groups.

	PE n=60	Control group n=120	OR	95%CI	p
	Observed n (%)	Observed n (%)			
Genotype C3435T					
CC	18(30.00)	37(30.83)	0.96	0.46-1.97	0.53
CT	30(50.00)	66(55.00)	0.98	0.51-1.89	0.54
TT	12(20.00)	17(14.17)	1.51	0.613.67	0.21
Allele					
C	66(55.00)	140(58.33)	0.87	0.55-1.39	0.31
T	54(45.00)	100(41.67)	1.14	0.72-1.82	0.31
Genotype G2677T/A					
GG	19(31.67)	42(35.00)	0.86	0.42-1.74	0.39
GT	31(51.67)	67(55.83)	0.85	0.43-1.65	0.36
TT	7(11.67)	9(7.50)	1.62	0.49-5.20	0.25
TA	1(1.67)	2(1.67)	1.00	0.05-59.9	0.71
GA	2(3.32)	0	-	-	-
AA	0	0	-	-	-
Allele					
G	71(59.17)	151(62.92)	0.85	0.53-1.37	0.28
T	46(38.33)	87(36.25)	1.09	0.67-1.75	0.39
A	3(2.50)	2(0.83)	3.05	0.34-36.87	0.21

Table II. Comparison of genotypes of C3435T MDR1 polymorphism in PE and control groups with the clinical and biochemical parameters.

Parameters	Genotype C3435T	n	Mean
Systolic blood pressure (mmHg)	CC	18	157.78±5.00
	CT	30	159.50±3.49
	TT	12	169.17±6.06
Diastolic blood pressure (mmHg)	CC	18	104.44±3.36
	CT	30	99.83±2.26
	TT	12	107.50±3.05
Age (years)	CC	18	29.44±1.21
	CT	30	29.67±0.89
	TT	12	28.92±1.76
Height (cm)	CC	18	164.71±1.91
	CT	30	164.60±1.09
	TT	12	166.08±1.63
Body mass before pregnancy (kg)	CC	18	66.00±5.02
	CT	30	63.97±2.42
	TT	12	64.00±4.04
Body mass in pregnancy (kg)	CC	18	80.59±5.04
	CT	30	79.87±2.43
	TT	12	82.42±4.27
Number of pregnancies	CC	18	1.33±0.14
	CT	30	1.57±0.16
	TT	12	1.75±0.28
Completed week of pregnancy	CC	18	34.89±0.92
	CT	30	32.90±0.63
	TT	12	33.25±1.23

Discussion

Numerous studies focused on the influence of MDR1 polymorphisms on morbidity and course of cancers. The increased susceptibility to certain cancers in carriers of MDR1 mutated variants is the result of weakening of protective role of P-glycoprotein against xenobiotics.

In placental barrier the number of transport proteins responsible for the communication between mother and fetus has been identified. These proteins allow the penetration of nutrients from mother to fetus and the removal of wastes in the opposite direction. Among these transporters have also been identified proteins from ABC superfamily including P-glycoprotein. This protein protects the developing fetus against access of xenobiotics, therefore function of P-glycoprotein in placenta has the protective effects [5].

Number of polymorphisms of P-glycoprotein gene has been

analysed to determine their possible effects on protein expression and on function of placental barrier. This process provides communication between the mother and the developing fetus [5]. The influence of C3435T and G2677T/A polymorphisms on the P-glycoprotein expression in placenta has been shown in several studies. Hernauer et al. observed the decreased P-glycoprotein expression in placenta of women carriers of mutated 3435T and 2677T/A alleles. This could be the reason of decrease placental fetoprotection in pregnant women [14]. A similar relationship was observed by Hitzl'a et al. [15]. Furthermore, the study of Tanabe'a et al. confirmed the reduced expression of placental P-glycoprotein in patients carriers of 3435T and 2677T/A variants (statistically not significant) [16].

There are papers regarding the influence of MDR1 polymorphisms on the transplacental transport of drugs belonging to P-glycoprotein substrates. Rahi et al. examined the

Table III. Comparison of genotypes of G2677T/A MDR1 polymorphism in PE and control groups with the clinical and biochemical parameters.

<i>Parameters</i>	<i>Genotype G2677T/A</i>	<i>n</i>	<i>Mean</i>
Systolic blood pressure (mmHg)	GG	19	153.95±4.65
	GT	31	162.58±3.79
	TT	7	168.57±5.95
	TA	1	170.00±0.00
	AA	2	170.00±10.00
Diastolic blood pressure (mmHg)	GG	19	99.74±3.16
	GT	31	102.26±2.26
	TT	7	110.00±3.78
	TA	1	100.00±0.00
	AA	2	115.00±5.00
Age (years)	GG	19	29.68±0.92
	GT	31	29.94±1.01
	TT	7	27.71±2.48
	TA	1	28.00±0.00
	AA	2	26.50±2.50
Height (cm)	GG	19	161.95±1.81
	GT	31	165.87±0.91
	TT	7	167.43±2.27
	TA	1	166.00±0.00
	AA	2	170.00±5.00
Body mass before pregnancy (kg)	GG	19	65.84±4.71
	GT	31	64.53±2.44
	TT	7	63.28±5.45
	TA	1	65.00±0.00
	AA	2	57.00±2.00
Body mass in pregnancy (kg)	GG	19	79.79±4.78
	GT	31	81.77±2.54
	TT	7	79.57±4.53
	TA	1	86.00±0.00
	AA	2	71.50±1.50
Number of pregnancies	GG	19	1.42±0.16
	GT	31	1.65±0.18
	TT	7	1.43±0.20
	TA	1	2.00±0.00
	AA	2	1.00±0.00
Completed week of pregnancy	GG	19	33.74±0.91
	GT	31	33.13±0.66
	TT	7	33.86±1.68
	TA	1	33.00±0.00
	AA	2	38.00±2.00

relationship between the C3435T and G2677T/A polymorphisms of MDR1 gene and placental transfer of antipsychotic drug called quetiapine. They found that the 3435T allele is associated with much larger transfer of quetiapine which may confirm the reduction in placental expression of P-glycoprotein in the presence of this allele [17].

Recently, it was demonstrated the possible influence of PE pathological processes on of the blood-brain barrier function. The analysis was performed on a small population of pregnant women, however it was proved much less effective action of this barrier in women with pregnancy induced hypertension compared to healthy pregnant women. The authors suggest that the reduced permeability in the blood-brain barrier may be associated with neurological symptoms such as seizures occurring in the course of eclampsia [18]. In the etiology of pregnancy induced hypertension, the importance of abnormalities of in the placenta at the stage of formation of utero-placental circulation is also emphasized [19]. Analyzing the relationship between two described the barriers, it should be noted that in physiological conditions, P-glycoprotein expression in the placental and blood-brain barrier is increased.

Numerous reports confirm the existence of ethnic differences in the prevalence of C3435T and G2677T/A polymorphisms of MDR1 gene. Ameyaw et al. analyzing the MDR1 C3435T polymorphism found that in African populations, the C allele is much more common. The frequency of this allele in the Ghanaian, Kenyan, Sudanese population and the black population of the United States were 83%, 83%, 73% and 84%, respectively. According to some researchers, the C allele occurs much less frequently in the Caucasian and Asian populations [20].

The results obtained by Schaeffler'a et al. confirmed higher frequency of C3435T polymorphism in African populations. Among the inhabitants of West Africa, the 3435CC genotype was found in 83% of cases. The authors also examined the frequency of this polymorphism in Caucasian obtaining much lower value of 26% [21].

According to Balram'a et al. studying the distribution of C3435T polymorphism in Asian populations, frequency of 3435C allele in group of Chinese and Malays presented as in Caucasians. However, in the Indian population, the researchers found lower incidence of C allele [22]. The frequency of C3435T polymorphism obtained in our study is comparable with the distribution in other Caucasian populations. This observation is consistent with the conclusions obtained by other authors.

Yi et al. showed that the frequency of 2677A allele of G2677T/A polymorphism is significantly higher in Asian populations and reaches up to 20% [23]. This variant is much less common in African-Americans [24]. The prevalence of G2677T/A polymorphism of MDR1 gene is comparable with results obtained by other investigators analyzing the Caucasian population.

On the basis of several studies, the detected differences in the prevalence of these polymorphisms should lead to the use of an individual dosage regimen of P-glycoprotein substrates which depends on the degree of expression of this protein. In pregnant patients using pharmacotherapy it should take into account the relationship between the above polymorphisms and the degree of expression of P-glycoprotein in the placenta. Individualization of pharmacotherapy based on the level of expression of

P-glycoprotein may determine its effectiveness and safety of the mother and developing fetus [5].

The current state of research allows to determine the impact of examined polymorphisms on the expression of P-glycoprotein in placenta which is an important part of barrier ensuring the communication between mother and fetus. The presence of specific variant of C3435T and G2677T/A polymorphism leading to reduced expression of this protein in placenta influences the degree of penetration and fetal exposure to toxins, teratogenic substances including drugs used in preeclampsia. It has a substantial impact on the proper course of pregnancy [25, 26, 27].

Conclusions

In our study comparing the frequency of different genotypes and alleles of C3435T and G2677T/A polymorphism of MDR1 gene it was shown no statistically significant differences between women with PE and control group. Moreover, there was no statistically significant correlation between the occurrence of individuals genotypes of examined polymorphisms and clinical and biochemical parameters in women with PE. However the interesting tendency to higher prevalence of mutated 2677A allele of G2677T/A MDR1 polymorphism in PE group has been shown. For this reason further analysis of genetic variants of P-glycoprotein is recommended including also the modulating effect of hormones and some interleukins in the development of PE pathology.

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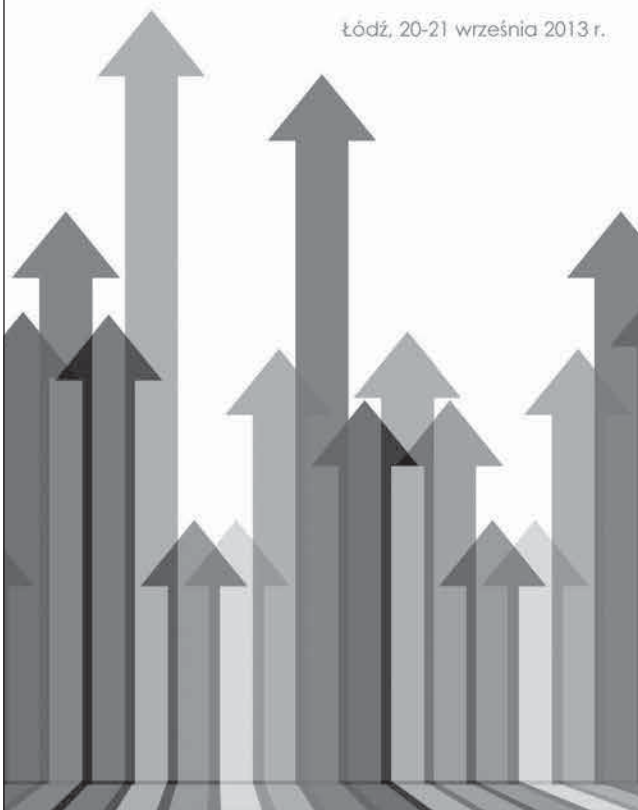


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