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Correlation of Catechol-o-methyltransferase Val158met Gene Polymorphisms in Severe Preeclampsia in Manadonese – Indonesian Population

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ABSTRACT

Preeclampsia is a pregnancy-specific disorder causing great morbidities and mortalities to date, clinicians have long been looking for specific methods to predict preeclampsia in women. Recent study of polymorphism of Catechol-O-methyltransferase (COMT) shows that there is a decrease in the expression of COMT in the placenta of preeclamptic patient that might be used as a predictor for preeclampsia. This study was an analytic cross sectional in 20 pregnant women with severe preeclampsia and 20 women with normal pregnancies in the Department of Obstetrics Gynecology, Prof. dr. R.D. Kandou Hospital Manado which fulfil the study criteria. After anamnesis and physical examination, the subjects' blood serum was taken and screened by PCR to assess the COMT Val 158Met gene polymorphisms. Most of the subjects of this study are multiparous (65% in normotensive and 70% in severe preeclampsia), gestational age > 37 weeks (45%) in normotensive and 29-36 weeks (50%) in severe preeclampsia, high school education (85% in normotensive and 60% in severe preeclampsia), and housewife (85% in normotensive and 70% in severe preeclampsia). After analysis, we found a significant correlation between the incidence of severe Preeclampsia with COMT Val158Met gene polymorphisms, p = 0.031 and OR = 7.36 (95% CI = 1.34 to 40.55). There is a significant correlation between the incidence of severe Preeclampsia with COMT Val 158Met gene polymorphisms, and those who have the COMT gene polymorphism is at risk 7.4 times more likely to suffer severe preeclampsia.

1. INTRODUCTION

Preeclampsia is a pregnancy-specific disorder that complicates approximately 4-8% of all pregnancies [1], [2]. Preeclampsia is the leading cause for maternal and neonatal mortality throughout world [3]. The effect on pregnant women varies from mild preeclampsia, severe preeclampsia / hypertensive crisis, eclampsia

and hemolysis elevated liver enzymes low platelet count syndrome (HELLP), while the impact of these abnormalities in the fetus also varies from premature birth, growth retardation (IUGR) and fetal death [1], [4]. The incidence of preeclampsia in the world in nulliparous population of approximately 5-10% [5]. In the United States, the complications of preeclampsia occur approximately 5% of all pregnancies [4]. The incidence of preeclampsia in RSCM Jakarta in 2011 was 16.4% [6]. Preeclampsia is one of the three leading causes of death after bleeding and infection. In 2011, they became one of the most common cause of maternal mortality, preterm delivery, intrauterine growth restriction and the causes of morbidity and mortality in neonates [7– 11]. Based on previous research, according to preeclampsia was found to have a genetic component. Genetic studies of single nucleotide polymorphisms (SNPs) in genes encoding nitric oxide synthase (NOS3) associated with risks of preeclampsia and the severity of complication [12]. Recent study of polymorphism of Catechol-O-methyltransferase (COMT) shows that there is a decrease in the expression of COMT in placental of preeclamptic patient [13]. Enzyme which was first described in preeclampsia are enzyme-catalysed O-methylation of catecholamines and other catechol. They were explained in the late 1950s that these enzymes are responsible for the O-methylation, and Catechol-O-methyltransferase (COMT), most purified and characterized by the same group. Degradation pathways of estrogens and catecholamines need COMT as the key enzymes. The interest in COMT re-emerged in the late 1980s when COMT second generation of potent and selective inhibitors were developed and soon the structure of the two isoforms of COMT and COMT gene are characterized by polypeptides diclon [14], [15]. In studies, COMT gene G675A polymorphism in the population in Mexico is found elevated in women with hypertension in pregnancy compared with control group. [14] conducted a meta-analysis of 6 eligible studies and obtained that COMT VAL158Met polymorphism is positively associated with increased risk of preeclampsia ($p < 0.05$) [15]. Therefore, a decrease in the expression of COMT in the placenta of preeclamptic women might be used as a predictor for preeclampsia.

2. Methods

This research was a cross-sectional study of 40 subjects in the Department of Obstetrics and Gynecology, Prof. Dr. R.D Kandou Hospital Manado. Subjects in this study were patients with severe preeclampsia and normal pregnancy, each 20 subjects who meet the criteria and have signed the informed consent. The study had been approved by the ethical committee. Inclusion criteria for this study were pregnant women > 20 weeks, with severe preeclampsia including superimposed preeclampsia and willing to participate in research. Pregnant women with diabetes mellitus, kidney disorders, heart disorders, chronic hypertension, premature rupture of membranes, clinical signs of infection, multiple pregnancy, fetal death in utero were excluded in this study. After anamnesis and physical examination, the subjects blood serum were taken as much as 5 cc, stored in a sample bottle, and then sent to the Prodia laboratory to be sequenced by PCR Verify Thermal Cycler, Applied Biosystems, a sequencing tool AB3500 Genetic Analyzer, Life Techonologies, reagents extraction High Pure PCR Template Preparation Kit product Rche Applied Biosystems, CAT 11796828001, Lot: 10957800, ED: 30-04-2016 and PCR reagents Robust 22G Kapa Kapa Biosystems Taq Polymerase product, Cat: KK5005, Lot: -, ED -.

3. Results

Table 4.1 shows subject obtained in this study most are multiparous (65% in normotensive and 70% in severe preeclampsia), gestational age> 37 weeks (45%) in normotensive and 29-36 weeks (50%) in severe preeclampsia, high school education (85 % in normotensive and 60% in severe preeclampsia), and is a housewife (85% in normotensive and 70% in severe preeclampsia). The Chi square test $\chi 2 = 6.14$, $p = 0.031$, which means there is a significant relationship between the incidence of severe preeclampsia with the COMT Val158Met gene polymorphism and the odds ratio (OR) = 7.36 (95% CI = 1.34 to 40.55), which means they have the COMT Val158Met gene polymorphism at risk 7.4 times more likely to suffer severe

preeclampsia compared to those who do not have COMT Val158Met gene polymorphism.

Table 4.1 Subjects Study Characteristic

Characteristic	Normotension		Severe Preeclampsia	
	n	%	n	%
Parity				
Primiparity	7	35	6	30
Multiparity	13	65	14	70
Gestational Age				
≥ 20 – 28 weeks	5	25	1	5
29-36 weeks	6	30	10	50
≥ 37 weeks	9	45	9	45
Education				
Bachelor	0	0	2	10
Diploma	0	0	0	0
Senior High School	17	85	12	60
Junior High School	3	15	3	15
Elementery	0	0	3	15
Pekerjaan				
PNS	0	0	1	5
Entrepreneur	3	15	4	20
Students	0	0	1	5
Housewife	17	85	14	70

Table 4.2 Statistic analysis based on nucleotide changed COMT Val 158Met gene in severe Preeclampsia

	Normotension		Severe Preeclampsia		
	N	%	n	%	*P**)
AUG	2	10	9	45	0.031
GUG	18	90	11	55	
Total	20	100	20	100	

*) Chi Square Test

Table 4.3 Statistic analysis based on Alelle location COMT Val158Met gene in severe Preeclampsia

Polimorfisme	Normotension		Severe Preeclampsia		
	N	%	n	%	*P**)
(+ / Val-Met)	2	10	9	45	0.031
(- / Val-Val)	18	90	11	55	
Total	20	100	20	100	

*) Chi Square Test

4. Discussion

Genetic influence in preeclampsia has long been known but how the genes involved is not known directly. Studies are still conducted to find out the genetic components that are involved in the process of preeclampsia. However, the recent study of polymorphism of Catechol-O-methyltransferase (COMT) showed that a decline in placental COMT expression in preeclampsia [8], [9]. In this study, we conducted an assessment of the correlation between COMT Val158Met gene polymorphism with severe preeclampsia patients in Prof. Dr. R. D. Kandou Hospital Manado. Pregnant women over 20 weeks of pregnancy with high blood pressure accompanied by proteinuria is characterized by preeclampsia Research by showed that COMT associated with blood pressure regulation and deficiency of the COMT activity will cause hypertension in animal research subjects. COMT deficiency led to the absence of a 2-methoxyoestradiol (2-

ME), a natural metabolite of oestradiol increased during the third trimester of a normal pregnancy in humans. 2-ME improves the condition of preeclampsia without toxicity in pregnant rats and suppress placental hypoxia, increase hypoxia inducible factor -1A and sFlt-1. COMT and 2-ME levels ware significantly lower in women with severe preeclampsia [16]. Nowadays, research on COMT Val 158Met gene polymorphisms has been conducted to determine changes in blood pressure and hypertension in humans. Coding sequence of the COMT polymorphism makes the nucleotide G to A that turns valine amino acid into methionine at position 158. 158Met COMT variant has lower stability and showed lower enzyme activity. Currently, the preeclampsia may be associated with the COMT gene polymorphism, but the genetic study of these polymorphisms remains to be investigated farther [13]. In a previous study, found that the population of Chinese women with the COMT variant alleles (158Met) have an increased risk of preeclampsia [17]. Meta-analysis conducted by, from the six studies conducted in Chinese, Korean, Mexican, Spanish, and Norwegian population found that COMT Val158Met gene polymorphism carriers have higher risk on incidence of preeclampsia. Study by inspired by the research hypothesis that COMT deficiency associated with preeclampsia. They assess the potential role of high and low activities of haplotypes in the central part of COMT. Their research subjects were identified via Nord-Trandelag Health Study (HUNT2) retrospectively, singleton pregnancies of women with preeclampsia and non-preeclampsia (as a control) cohort taken from the Medical Birth Registry of Norway (MBRN) database. They found 1135 women who registered with preeclampsia and 2262 control pregnancies. According to, single nucleotide polymorphisms of genes (single nucleotide polymorphisms / SNPs) COMT show significant effects on the activity of the enzyme. Therefore, the hypothesis that these SNPs in genes related to the pathogenesis of preeclampsia [15], [18], [19]. Table 4.2 showed statistical analysis based on changes nukleutida single Val158Met gene COMT in women with severe preeclampsia G to A occur in two normal pregnancies (10%) and 9 in pregnancies with severe preeclampsia (45%), While that has not changed in 18 normotensive pregnancies (90%) and 11 in severe preeclampsia (55%), and the Chi square test $\chi 2 = 6.14$, $p = 0.031$.

Table 4.3 showed the statistics based on the location of alleles Val158met gene COMT in women with severe preeclampsia and normotensive pregnant women. It showed 20 pregnant women normotensive only 2 (10%) occurring polymorphisms of COMT Val158Met whereas in pregnant women with severe preeclampsia are 9 people (45%) occurring polymorphisms COMT Val158Met. This suggests a significant correlation between COMT polymorphism Val158Met with severe preeclampsia incidence with $p = 0.031$ (OR = 7.36; 95% CI = 1.34 to 40.55). These results are consistent with the research conducted by in female population Southwest China. They examine the COMT genotype polymorphism analysis by Polymerase Chain Reaction-Restriction Length Polymorphism (PCR-RFLP). They examined the COMT gene polymorphism in 187 DNA Preclampsia pregnant women and 189 women with normal pregnancies. They have 80% ability of sample size to detect vulnerable locus with a relative risk > 2.3. There were significant association of Val158Met COMT polymorphism in preeclampsia patients compared with controls ($p = 0.031$ and 0.015) and the risk of preeclampsia Odd Ratio was 2.395 (95% CI = 1.061 to 5.408). AA genotype and the Met variant of the COMT gene val158Met at significantly higher in pregnancies with preeclampsia compared with normal pregnancy (both $p < 0.05$). They also assessed the relationship with mild preeclampsia and severe preeclampsia, but there was no significant change ($p = 0.600$) [20].

5. Conclusion

In this study shows that there is a significant correlation between COMT polymorphism Val158Met with severe preeclampsia incidence. We hope this research can be used as a marker to identify pregnant women which are genetically prone to preeclampsia.

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7. References

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Attachment

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HASIL PEMERIKSAAN
Polimorfisme Gen COMT Val158Met (rs4680)
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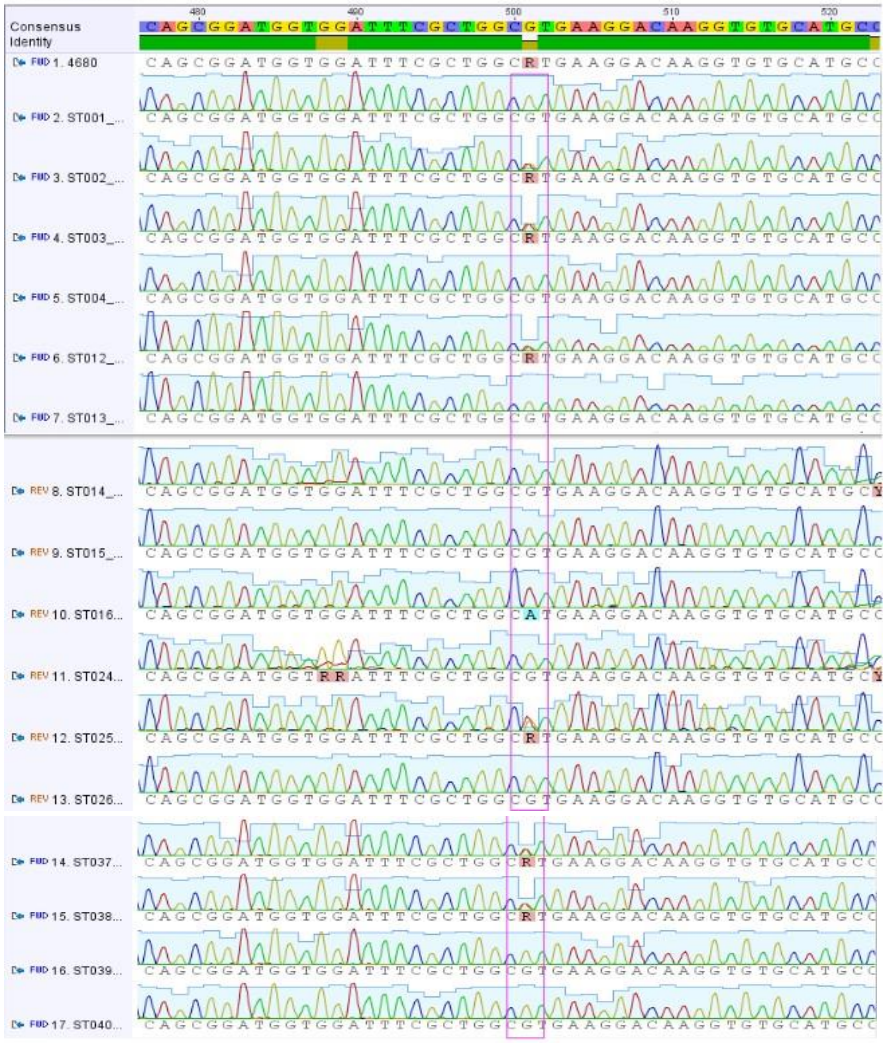
Hasil Sequencing



Jakarta, 7 Juli 2015

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