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Polymorphisms of the *IL1-BETA-511T/C* gene in pregnant women complicated with pre-eclampsia

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Objective Identify the association between single nucleotide polymorphisms (SNP) of IL-1 Beta and the onset and severity of the disease. Pre-eclampsia (PE) is a relatively common, systemic pregnancy disorder characterized by the development of concurrent hypertension (>140/90 mmHg) and proteinuria (>300 mg/24 h) at ≥20 weeks of gestation, that may also be associated with a myriad of other symptoms such as edema, headache, blurred vision, irritability, abdominal pain, and thrombocytopenia.
Methods The extracted DNA was amplified for IL-1 Beta RFLP in 60 clinically diagnosed preeclampsia pregnant women and 60 normotensive pregnant women. For statistical significance, OR was measured and all data were processed by using SPSS.
Results IL-1 Beta genotyping in PE pregnant women showed the following results TT genotype having 2.33 fold risk of having PE and etiological factor (0.57) while TC mutant genotype showed 1.125 fold risk of having PE etiological factor of (0.111), while homozygous CC genotype considered as protective genotype with protective factor of (0.674). T allele considered the etiological factor of (0.287) while C allele considered as protective allele with protective factor of (0.589).
Conclusion IL-1 Beta T allele considered as significant risk factor for having preeclampsia. The presence of IL-1 Beta C alleles protects against having preeclampsia.
Keywords preeclampsia, IL-1 Beta RFLP

Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome, characterized by the new onset hypertension and proteinuria after the 20th week of gestation. PE occurs in about 5–7% of all pregnancies in the world, which is a leading cause of the maternal and fetal mortality and morbidity.[1] Despite extensive efforts to evaluate the mechanisms and molecules of PE, the underlying pathogenesis of PE has not yet been fully elucidated. Epidemiological research indicated that the PE was associated with the family and genetic control, and inheritance appeared to have a major function in the pathology of this disease.[2] Moreover, PE is a multiple gene disorder, affected by genetic and environmental factors, like interaction between maternal and fetal genes, which were important determinants of maternal disease susceptibility.[3] Therefore, genetic factors cannot be ignored in the pathogenesis of PE. Despite the etiology of PE remains unknown, a growing evidences indicated that the inflammatory response might explain the development of the PE.[3] It was reported that the normal pregnancy was regarded as a mild inflammatory state,[4] while PE was considered to be an exaggerated inflammatory state.[4,5] Furthermore, PE had been proposed to be a complicated systemic inflammatory response acting in network, which contained not only the endothelium but also the inflammatory immune cells, the clotting and the complementary systems, metabolic and other changes mainly regulated by cytokines.[6] During pregnancy, many cytokines are secreted by immune cells and lymphocytes at the interface of trophoblast and decidua, which mainly mediate and regulate immunity, inflammation and hematopoiesis. Benyo et al. indicated that several cytokines had been found to be increased in pregnant women with PE. The serum level of inflammation cytokines, one kind of cytokines, such as IL-1β, IL-2, IL-6 and IFN-c had been found to be higher in women with PE than in normotensive pregnant women,[7–9] which leaded to harmful Th1 immunity, threatening pregnancy by generating cytotoxic factors that injured maternal endothelium, altered steroid hormones biosynthesis and affected other factors which were implicated in trophoblast invasion and maternal spiral artery remodeling.[10,11] The production of inflammatory cytokines is regulated by the cytokine gene, thus, the cytokines gene polymorphism may play a key role in the development of PE. IL-1β is a pro-inflammatory cytokines, belonging to the IL-1 system, which is an important role in mammalian reproduction. It had been reported that IL-1β had been implicated in the pathogenesis of PE.[12] Many researchers had found that the plasma level of IL-1β was elevated in preeclamptic women.[9,13–15] And increased placental expression of IL-1β was also observed in several researches.[13] IL-1β is located in 70–110 kb region of chromosome 2q13–21, including 7 exons and 6 introns. At least 20 SNPs have been reported in the region of IL-1β, among which -511 and -31 loci in the promoter region of IL-1β were two important single nucleotide polymorphisms, whose gene polymorphism could influence the gene transcription and lead to the function changes.[16] Moreover, the SNPS 2511 and 231 cites have been repeatedly associated with cardiovascular diseases.[16] The genotypic distribution of the IL-1β at position +3954 in exon and the IL-1β-511 C/T polymorphism respectively in Hispanic population, Dutch population and Taiwanese women, similarly, they all found no significantly statistical at the loci between the PE and normal pregnant women.[17–19]

Patients and Methods

Patients

The current study was conducted during the period from the first of February 2016 to the first of December 2016. Sixty patients who attended the outpatient and inpatient department, were diagnosed by a women consultant in the Maternity and Childhood Teaching Hospital on the basis of blood pressure measurement and proteinuria elevation. All subjects within the age group of 16–40 years were selected for the study. The PE diagnosis was based on the criteria from the report of the 'National High Blood Pressure Education Program, and 60 healthy controls, were included in the study. Blood pressure was measured with a mercury sphygmomanometer and the Korotkov sound technique. Diastolic pressure was indicated by the Korotkov V. sound. All patients had proteinuria ≥3 + or 4+ tested by dipstick in at least two random urine specimens obtained at least 4 h apart (according to the kit 3+ = 300 mg/day, 4+ = 1000 mg/day). Medical history, maternal age, gestational age were recorded.

Selection Criteria of Patients

Inclusion criteria

All subjects within the age group of 16–40 years were selected for the study. PE was defined as persisting elevated diastolic blood pressure (≥90 mmHg), a proteinuria (≥300 mg in a 24 urine samples) and the presence of edema. Subjects willing to participate were included in the study.

Exclusion criteria

Subjects with non-confirmed PE, essential hypertension, malaria, haemolytic anemia, any other infection such as urinary tract infection or upper respiratory tract infection, fetal death, renal disease, uterine malformation, *in vitro* fertilization treatment, placental abruption, infection, cancer, gestational diabetes mellitus, or any other systemic disease, including pre-existing hypertension, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) were excluded from the present study.

Selection Criteria of Control Groups

Inclusion criteria

Normotensive pregnant women had systolic/diastolic blood pressure below 120/80 mmHg, normal protein urea and blood urea and no history of hypertension or proteinuria. All pregnant women showed gestational age from 20 to 40 weeks.

Exclusion criteria

Exclusion criteria for healthy control were chronic hypertension, homeostatic abnormalities, cancer, diabetes mellitus, cardiovascular, autoimmune, renal and hepatic diseases, and anticoagulant therapy. All normotensive pregnant women have no systemic disease or chronic disease. In addition, they have no dead baby or history of dead baby.

Collection of Sample

Blood sample

Blood samples were collected from pregnant women included in the present study by venipuncture. A total of 6 ml of blood was drawn from forearm vein. Of 6 ml, 2 ml for GOT, GPT and ALP and 2 ml for blood urea and the rest 2 ml sample in EDTA tubes which was immediately deeply frozen for *IL-1Beta* SNP analysis.

Urine collection

For pregnant women and in most identical situations, a midstream clean-catch technique is usually adequate. 10 ml of urine for protein urea detection was required.

Genotyping

DNA was extracted with standardized DNA-extracting protocols using AccuPrep®Genomic DNA extraction kit (Bioneer. Korea). The amount of used blood samples for the DNA extraction was 200 µl. The PCRs were performed in a final volume of 50 µl containing 40 µl PCR buffer, and sense and antisense primers, 2.5 µl of each. We used 5 µl DNA per PCR reaction all mixed in master mix tubes AccuPower™ PCR PreMix Taq DNA polymerase dNTPs (dATP, dCTP, dGTP, dTTP) Tris-HCl pH 9.0, KCl, $MgCl_2$ Stabilizer and Tracking dye. The investigated DNA sequences were amplified by the following primers: IL-1β-511 locus: forward: 5′-TGGCATTGATCTGGTTCATC-3′ and reverse: 5′-GTTTAGGAATCTTCCCACTT-3′. The condition of PCRs was as follows: The PCR conditions of -511T/C polymorphism of IL-1β were initial denaturation at 94°C for 5 min; 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s and extension at 72°C for 30 s and final tension at 72°C for 7 min. Then the PCR fragment was digested by AluI enzyme at 37°C for 1 h in a reaction volume of 10 mL. Digested products were separated by electrophoresis on a 2.5% agarose gel and visualized by Goodview staining. The expected results of IL-1β-511T/C are digested into 3 expected results: TT shows one band with 518 bp, CC shows two bands with 403 bp and 115 bp, TC shows three bands with518 bp, 403 bp and 115 bp.

Data Analysis

Hardy–Weinberg equilibrium of the tested SNP was calculated. Logistic regression analysis was used for the analysis of the association between IL-1β-511T/C genotype and risk of PE. Multiple linear regression analysis was used to test the association between carrier state of IL-1β-511T/C genotypes and diagnosis of hypertension and proteinuria. The associations were adjusted for maternal age, gestational age. All calculations were performed with the statistical software package SPSS 23.

Results

The results presented in this study were based on the analysis of a random 60 pregnant women with an established diagnosis of PE, their age ranged between 16 and 39 years with a mean of 27.75 years. Also a 60 apparently healthy pregnant as control group was selected according to maternal and gestational age of the patients group. Their age ranged between 16 and 40 years

with a mean of 30.2 years. The patients group was further subdivided into two subgroups according to their gestational age at which the hypertension and proteinuria appear into early onset PE, and late onset PE. So, early onset PE started before 35 week of gestation and the late onset of PE appear after 35 week of gestation, the early onset represent 30 cases with gestational age range (24–34) weeks and mean of 27.9 while the late onset (30 cases) with a gestational age range between 36 and 39 week and mean of 36.7. In addition, the gestational age mean of the studied group was statistically significant with ($P < 0.05$) (Table 1).

The frequency of PE patient who have a history of PE in previous pregnancy (45%), and history of dead baby in pervious pregnancy was (35%) which represent a high percentage of cases. Family history frequency was represented (66.6%) which have sister or mother history of PE, as in Table 2.

The diastolic Blood pressure measurement of the PE patients ranged between 90 and 150, in the early onset PE the diastolic blood pressure ranged between100 and 110 mmHg and mean of (101 mmHg), while in the late onset PE ranged between 90 and 150 mmHg with a mean of (118 mmHg) when compared to the healthy control group the diastolic blood pressure range between 70 and 80 mmHg with a mean of 75.5 mmHg. The diastolic blood pressure mean was statistically higher in PE patient when compared to the control group with *P* value (0.001). Regarding the systolic blood pressure in early onset PE patients ranged between 140 and 160 mmHg with a mean of (163 mmHg), while in the late onset ranged between 130 and 200 mmHg with a mean of (149 mmHg).

Table 2 **Frequency distribution of preeclampsia cases by family history, and patient history**

		Number	%
1.	Family history of Preeclampsia		
	Negative	20	33.3
	Positive	40	66.6
	Total	60	100
2.	Patient history of Preeclampsia in previous pregnancy		
	Negative	33	55
	Positive	27	45
	Total	60	100
3.	History of dead baby		
	Negative	39	65
	Positive	21	35
	Total	60	100

Table 1. **Description of the three study groups by maternal age, gestational age and party**

		Preeclampsia cases				Healthy control		P-value
		Early onset		Late onset				
		No.	%	No.	%	No.	%	
1.	**Maternal age (years)**							0.042[NS]
	16–26	11	36.7	18	60	29	48.3	
	27–37	12	40	5	16.7	13	21.7	
	≥38	7	23.3	7	23.3	18	30	
	Range	16–39		17–37		20–40		
	Mean	30.6		25.7		30.2		
	SD	7.28		7.2		7.79		
	SE	1.32		1.3		1.006		
	Total	30	100	30	100	60	100	
2.	**Gestational age (weeks)**							<0.05
	<35	30	100	–	–	41	86.3	
	≥35	–	–	30	100	19	31.7	
	Range	24–34		35–39		23–39		
	Mean	27.9		36.7		31.16		
	SD	4.26		0.9		5.53		
	SE	0.78		0.2		0.718		
	Total	30	100	30	100	60	100	
3.	**Parity**							0.178[NS]
	Multiparous	11	36.6	14	46.6	43	71.44	
	Uniparous	19	63.4	16	53.4	17	28.8	
	Total	30	100	30	100	60	100	

No., Number; SD, Standard Deviation; SE, Standard Error; NS, Non-Significant.

The systolic blood pressure mean was statistically higher in PE patient when compared to the control group with *P* value (≤ 0.01) (Table 3).

Protein urea measurement among early and late onset of PE ranged from 300 to 1000 mg/24 h with mean of 790 in early onset and 486.7 in late onset when compared to healthy control which still normal with statistically significant *P* value (<0.01), Blood urea measurement among PE patient's showed significantly higher elevation when compared with healthy control, in the early onset PE blood urea measurement ranged from 67 to 120 mg/dl while the late onset ranged from 57 to 113 mg/dl when compared with healthy control with statistically significant *P* value (<0.05) as in Table 4.

Table 3. **The difference between three study groups in diastolic blood pressure and systolic blood pressure**

		Early onset	Late onset	Healthy control	*P* value
1.	**Diastolic blood pressure mmHg**				
	Mean	101	118	75.5	0.001
	Range	100–110	90–150	70–80	
	SD	3	26.8	5	
	SE	0.56	4.9	0.65	
	Total	30	30	60	

Bonferonni *t*-test for difference in mean between: Cases (PE) x Healthy Controls *P* Value = 0.001.

2.	**Systolic blood pressure mmHg**				
	Mean	163	149	125.33	≤ 0.01
	Range	140–160	130–200	120–130	
	SD	27.7	5.5	5	
	SE	5	1	0.7	
	Total	30	30	60	

Bonferonni *t*-test for difference in mean between: Cases (PE) x Healthy Controls *P* value ≤ 0.01, SD, Standard Deviation; SE, Standard Error.

Table 4. **The case-control difference in mean concentration of protienurea and blood urea**

	Preeclampsia cases		Healthy control	*P* value
	Early onset	Late onset		
Protein Urea Nitrogen mg/dL				<0.01*
Range	300–1000	300–1000	30–100	
Mean	790	486.7	41.7	
SD	326	314.8	26	
SE	59.5	57	3.4	
Total	30	30	60	

Bonferonni *t*-test for difference in mean between: Cases (Preeclampsia) x Healthy Controls <0.01

Blood Urea Nitrogen mg/dl				<0.05*
Range	67–120	57–113	11–23	
Mean	92	85	17	
SD	14.9	13.9	4	
SE	2.6	2.5	0.5	
Total	30	30	60	

Bonferonni *t*-test for difference in mean between: Cases (Preeclampsia) x Healthy Controls <0.05, SD, Standard Deviation; SE, Standard Error.

Genetic Study

DNA amplification

The products of successful binding between the extracted DNA and specific primers for *IL-1 Beta* gene were detected by gel electrophoresis analysis using DNA marker (100bp DNA ladder) and the product size was 518bp for both patients and control groups.

Detection of IL-1 beta gene polymorphism

The distribution of *IL-1Beta-511* polymorphism was detected by PCR-RFLP technique, at this locus there're three genotype; homozygote (CC) at 403bp, and 115bp, heterozygous (TC) at 518bp and 403bp, 115bp and wild type (TT) which still undigested 518bp the genotype distribution had no deviation from Hardy-Weinberg equilibrium in all study groups and agree with the previous reports[3] (Fig. 1).

As shown in Table 5, IL-1 Beta genotyping in PE pregnant women showed the following results TT genotype expressed (50%) of cases having 2.33 fold risk of having PE with *P* value of (0.04) and with etiological factor (0.57) while TC mutant genotype expressed (20%) and showed 1.125 fold risk of having PE with *P* value of (0.006) and etiological factor of (0.111), while homozygous CC genotype expressed (30%) and considered as protective genotype with *P* value of (<0.001) and protective factor of (0.674). T allele have 2.428 fold increase risk of having PE with *P* value of (0.001) and etiological factor of 0.287 while C allele considered as protective allele with *P* value of (0.001) and protective factor of (0.589).

Discussion

Interlukine-1beta is located on Chromosome 2q13-21 at location 70–110 kb, which include 7 exon and 6 intron.[20] IL-1β is a pro-inflammatory cytokine, secreted by monocytes, macrophages and epithelial cells, which implicates in a variety of

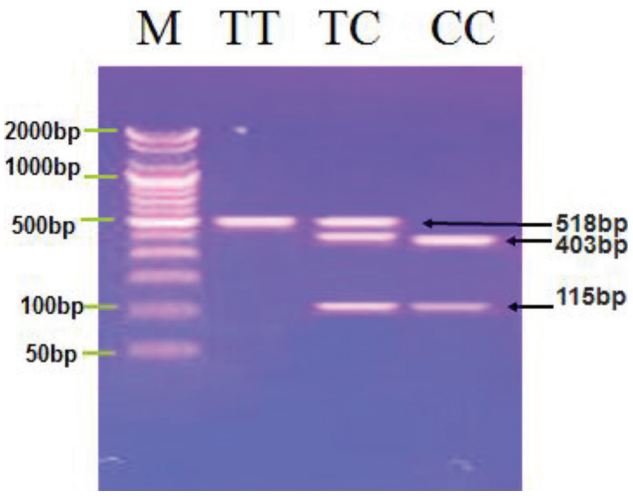

Fig. 1 **Agarose Gel Electrophoresis Image that Show the RFLP-PCR Product Analysis of *IL-1Beta* Gene by Using Alu I Restriction Enzyme from Some Blood Patient Samples and Healthy Control Sample. Where M: Marker (2000–50bp), Patient Samples as Homozygote (CC) at 403bp, 115bp. Patient Samples as Heterozygous (TC) at 518bp and 403bp, and 115bp. Patient and Control that Appeared as Wild Type (TT) which Still Undigested.**

Table 5. **Distribution of genotypes and alleles of *IL-1 Beta* Gene in case & control**

	PE cases no.(%)	Healthy control no.(%)	OR	Inverse OR	95% CI OR	*P* value	Adjusted P	EF	PF
IL-1Beta (-511) Polymorphism									
TT	30(50)	18(30)	2.3	0.4	1.1–4.9	0.04	0.04	0.57	***
TC	12(20)	26(43.3)	1.1	0.9	1.4–6.9	0.006	0.006	0.111	***
CC	18(30)	16(26.7)	0.326	3.1	0.4–1.9	<0.001	<0.001	***	0.674
Total	60(100)	60(100)							
Allele frequency (IL-1Beta -511)									
T-allele	72(60)	62(51.7)	2.4	0.4	0.8–2.3	0.001	0.001	0.287	***
C-allele	48(40)	58(48.3)	0.4	2.4	0.4–1.2	0.001	0.001	***	0.589
Total	120(100)	120(100)							

activities.[9,21] IL-1β has previously been found to increase the production of TNF-alpha, IL-6, HCG, which were proved to be associated with the development of PE.[9,21] IL-1β may also involve in the oxidative stress linked with PE by stimulating the secretion of other lymphocytotropic cytokines and catabolic enzymes.[3] In addition, IL-1β has been considered to be a potential mediator of maternal endothelial dysfunction in PE.[22] Beyond that, it has been shown that IL-1β played an important role in the abnormal extrarillous trophoblast invasion in PE.[23]

The positive association of *IL-1β-511* polymorphism with preeclampsia which is established against preeclamptic pregnant women and normotensive pregnant women as control group indicating that the T-511C polymorphism carry a significant risk for preeclampsia. There must be other risk factors or complementary mechanisms for the risky genes to operate and cause preeclampsia among preeclampsia cases.

The *IL-1β-511* genotypes were assessed for their role in predicting the risk of having preeclampsia, compared with a healthy control group. Table 5 shows the *IL-1β-511* genotypes, had significant predictive power. The T allele had the strongest association $P = 0.001$ and significantly increases the risk of having preeclampsia by 2.4 times compared to normotensive pregnant women. In the other hand C allele had significant association and considered as a protective allele among Preeclamptic pregnant women (40%, OR = 0.4). Both the heterozygous TC and the wild type TT genotypes increase the risk of the disease by 1.1 times, $P = 0.006$ and 2.3 times ($P = 0.04$), respectively. While the homozygous CC genotype showed a statistically significant protective effect. Occurrence reduces the risk of having preeclampsia by 3.1 times .The diagnostic criteria for preeclampsia that studied in the present study were the same as previous studies investigating for the role of IL-1β gene polymorphisms in the pathogenesis of PE.[3,19]

These results were highly comparable with a study conducted by Wang et al., which investigated the relationship between the -511T/C polymorphisms of the IL-1β and PE in Chinese population. It was worthwhile to note that the polymorphisms in the promoter region of the IL-1β were associated with the genesis of the PE ($P < 0.05$). After calculation of the value of OR, the pregnant women bearing the TT genotype of the -511 T/C polymorphism of the IL-1β was more susceptibility of experiencing the PE ($X^2 = 9.479$, $P = 0.002$, OR = 1.716, 95% CI = 1.215–2.424). As for allele, the -511 T allele was observed to be associated with a high risk of the PE, in the similar manner, also found evidences that the polymorphisms at the position -511 in the promoter region of the IL-1β were associated with PE. The IL-1β promote genotype TC were associated with the development of PE. Polymorphic analysis data of -511C/T in IL-1β studied in Wang et al., not only the genotypic distribution but also the allele frequency did show a significantly statistical difference among case and control groups (for genotypic distribution $X^2 = 9.687$, $P = 0.008$; for allele frequency $X^2 = 8.557$, $P = 0.003$). The subjects carrying the TT genotype had 1.716 fold risk of the PE compared with the women with TC and CC genotypes ($X^2 = 9.479$, $P = 0.002$, OR = 1.716, 95% CI = 1.215–2.424). The results of allele also showed that the T allele might be a risk factor of the PE ($X^2 = 8.557$, $P = 0.003$, OR = 1.4, 95% CI = 1.117–1.754).[3]

Kang et al., revealed that there was no any role of the polymorphism of the *IL-1β-511T/C* in the pathogenesis of PE, among Taiwanese Population and also conducted that the homozygotes (T/T) could not be observed in both severe preeclampsia and control groups and the allele frequency of T alleles was only 2.1% in women with severe preeclampsia group and 1.7% in normal controls.[19] Moreover, another two experiments also found the similar phenomenon respectively in Hispanic women[17] and in Holland population,[24] which were totally disagreed with the present study results. Because the ethnic difference might play an important role in disease-gene association studies, we cannot adopt the conclusion from other countries without our own studies in the Iraqi's pregnant women, while in the present study the bulk of cases in the TT genotype in preeclamptic cases. The reason for the present results could be the complex interactions among genetic and environmental factors.[18]

Nasr et al., have found evidences that the polymorphism at the position -511 in the promoter region of the IL-1β was not associated with PE in Egyptian population. Concerning -511T/C gene polymorphisms, there was a statistically significant difference between PE cases and healthy control studied regarding TT genotype (P value = 0.0196), but there were no statistically significant differences between PE cases and healthy control regarding CC or TC genotypes (P value = 0.3304 and 0.2660 respectively). which have disagreed with the present study results.[25]

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