ORIGINAL ARTICLE

Assessment of association between Duffy blood group phenotypes and susceptibility to develop preeclampsia and its severity

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ABSTRACT

Aim: To investigate the relationship between Duffy blood group and prevalence and severity of preeclampsia in pregnant women referred to Shiraz University of Medical Science affiliated hospitals.

Methods: This cross-sectional was conducted in the Hafez and Zeinabiyyeh hospitals. The study population consists of 53 preeclamptic women and 53 age-matched pregnant women without preeclampsia. Diagnosis of preeclampsia was conducted based on the American College of Obstetricians and Gynecologists (ACOG) criteria and preeclamptic women were divided to 2 subsets of preeclampsia with mild features and preeclampsia with severe ones.

Results: The results of current study showed no significant differences in frequency of different phenotypes of this blood group between the normotensive and preeclamptic patients (p-value= 0.094). Similarly, there was not any significant differences in prevalence of each type of Duffy phenotypes in two subsets of the preeclampsia (p-value= 0.831).

Conclusion: Day by day, the underlying pathologic pathways of formerly idiopathic diseases are being discovered. Genetic codes have been shown to highly affect these pathways, triggering a cascade that ends with the disease entity. However, our article does not support a significant association between different positive phenotypes of DARC and susceptibility to preeclampsia, these studies should be encouraged in order to delineate the underlying biologic pathways and their disruption in pathologic conditions.

Keywords: Duffy Blood-Group System; DARC protein, human [Supplementary Concept]; Pre-Eclampsia

INTRODUCTION

Preeclampsia is a multisystem disorder characterized by endothelial cell dysfunction and neutrophil activation[1]. It's defined as a hypertension developed at second half of pregnancy with either significant end-organ damage and/or proteinuria[2]. It has been reported that 2-8% of all pregnant women worldwide experience preeclampsia and its deleterious effects; Also, near to16% of maternal deaths are caused by hypertensive disorders[3]. Furthermore,preeclampsia can lead to lots of short-term and long-term complications in both mother and fetus. Acute maternal complications include: eclampsia, stroke, abruptio placentae, disseminated intravascular coagulation, HELLP syndrome, liver hemorrhage/rupture, pulmonary aspiration/edema, adult respiratory distress syndrome, acute renal failure, cerebral hemorrhage and even death[4,5,6]. Long-term maternal complications include: chronic hypertension, diabetes mellitus, chronic renal failure, coronary artery disease and neurologic deficit[7]. The fetal burden of the disease mainly results from placental hypoperfusion. Even though termination of pregnancy may reduce maternal and fetal mortality and morbidity, it would get rise to birth of a premature neonatewith neurological sequelae of preterm delivery[8].

It is thought that both genetic factors and environmental factorsplay an important role in disease susceptibility[9,10,11]. Besides, several maternal, fetal and fetomaternal mechanisms have been suggested for pathophysiology of preeclampsia; in these all mechanisms, abnormal development of placental vasculature early in pregnancy is involved[12,13,14,15]. However, there are still some gaps about the molecular pathway that are not fully understood[16,17]; in other words, the main trigger for abnormal development of placental tissue and the subsequent cascade of events remains unknown.

Duffy Antigen Receptor for Chemokines (DARC) which is known as Fy glycoprotein (FY), is supposed to be one of the effective factors in incidence of preeclampsia[18].This glycosylated membrane protein is ubiquitously found on surface of the red blood cells and endothelial cells of postcapillary venules[19,20]. Duffy antigen is a potent nonspecific receptors of a variety of different chemokines[21,22]; among these chemokines, Interleukin-8 (IL-8) is seen to be the most intensively ligand of the DARC[23] and it is one of the most important neutrophil chemoattractant and activators[24]. On the other hand, this interleukin, is reported to be at high levels during pregnancy and even increases significantly in a preeclamptic women compared to a normotensive pregnant[25,26,27-].

This probable relationship between preeclamptic event and Duffy antigen system has not been completely evaluated; therefore, this study conducted to investigate the relationship between Duffy blood group and prevalence and severity of preeclampsia in pregnant women referred to Shiraz University of Medical Science affiliated hospitals.

METHODS

This cross-sectional study was conducted in the teaching hospitals affiliated to Shiraz University of Medical Sciences, Hafez and Zeinabiyyeh hospitals. The data of this study was gathered between 21th of March, 2016and 20th March, 2018. The target patient group of the study were those patients referred to these two hospitals and diagnosed by preeclampsia in that period. The control group were chosen from age-matched pregnant women without preeclampsia referred there.

Diagnosis of preeclampsia was conducted based on the American College of Obstetricians and Gynecologists (ACOG) criteria[28]: these patients were labeled as preeclampsia if they have new-onset of hypertension after the week 20th of gestation (Systolic Blood Pressure(SBP) ≥140 mmHg or Diastolic Blood Pressure(DBP) ≥90 mmHg on two occasions at least four hours apart), accompanied with proteinuria (Protein ≥1+ in on dipstick or a protein: creatinine ratio of more than 0.3 in a spot urine sample) or new-onset of any of the followings:platelet count <100,000/µl, serum creatinine >1.1 mg/dL in the absence of other renal disease, liver transaminases at least twice the upper limit of the normal concentrations, pulmonary edema, cerebral or visual symptoms such as blurred vision, headache and etc. However, in absent of these signs and symptoms or proteinuria, if the patient had SBP ≥160 mmHg or a DBP ≥110 mmHg, she was included in the patient group of the study.

In this study, preeclamptic women were divided to 2 subsets of preeclampsia with mild features and preeclampsia with severe ones; women with SBP ≥160 mmHg or a DBP ≥110 mmHg and proteinuria were included in the severe group. Furthermore, those women with SBP ≥140 mmHg or DBP ≥90 mmHg (with or without proteinuria) were considered as preeclamptic patient with severe features only if they had at least one of the signs and symptoms of significant end-organ dysfunction:new-onset cerebral or visual disturbance, platelet count of less than 100,000/ µl, unstoppable severe and persistent right upper quadrant or epigastric pain with unknown cause,serum transaminase concentration ≥2 times upper limit of normal ,pulmonary edema andprogressive renal insufficiency (serum creatinine >1.1 mg/dL). Other women were categorized as preeclamptic patients with mild features.

2 milliliters blood sample was obtained from both preeclamptic and normotensive women in EDTA tubes and sent to the laboratory for determination Duffy blood group antigens. The method used for antigens identification was based on AGH Maestria IGG (DIAGAST, France).

Afterwards, collected data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) 24 software. Chi-squared test was used to compare the phenotype frequencies of Duffy blood antigens between two groups of preeclamptic patients and the controls. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 53 patients were admitted to obstetric ward of Hafez and Zeinabiyyeh hospitals as preeclamptic patient between 21th of March, 2016 and 20th March, 2018. The same number of participants were chosen from age-matched hospitalized patients without preeclampsia and they were included in the study as the controls. Of those preeclamptic patients, 36 (67.9%) patients were diagnosed as preeclampsia with mild features and the others had preeclampsia with severe ones (Table 1). Ages of participants ranged from 22 to 41 with the average of 30.01±4.6 years (p=0.56). In overall in our study, the most common phenotype was FYa with 38.6%, followed by FY(a+/b+) with 34.9% and FYb with 26.4% (Table 1). Statistical analyses showed no significant differences in frequency of different phenotypes of this blood group between the normotensive and preeclamptic patients (p-value= 0.094). Similarly, there was not any significant differences in prevalence of each type of Duffy phenotypes in two subsets of the preeclampsia (p-value= 0.831).

Table 1. The prevalence of different phenotypes of Duffy blood group among the patient and control group.

Status of the study participants	Phenotype			Total
	FYa	FYb	Double positive (FY(a+/b+))	
Normotensive	23(43.3)	12(22.6)	18(33.9)	53
Preeclamptic				
Mild	13(36.1)	10(18.8)	13(36.1)	36
Severe	5(29.4)	6(35.2)	6(29.4)	17
Total	41(38.6)	28(26.4)	37(34.9)	106

DISCUSSION

Duffy antigen, also known as Fy glycoprotein, is a membrane receptor playing as a mediator in chemokine signal transduction pathways[29]. Throughout these several recent decades, scholars have stared investigations about the clinical significance of blood groups other than ABO and Rh blood group systems; Duffy antigen system as well as other blood group systems has been worked up to clarify its participation in pathogenesis of several both inflammatory and non-inflammatory diseases.

Studies has documented the Duffy antigen to be involved in pathogenesis of a variety of diseases such as suppurative pneumonia, asthma,rheumatoid arthritis, CNS autoimmune diseases, etc[30-33]. In a study by Lee JS et al., DARC expression was showed to be increased in the lung pre- and postcapillary parenchymal vessels and alveolar septa in the course of a suppurative pneumonia[30]. In 2008, Candelaria Vergara et al. found the rs2814778 polymorphism in DARC gene to be associated with higher levels of IgE among certain populations of the African descent, predisposing them to higher prevalence of asthma and its severity[31]. In a study conducted by Emily Smith and her colleagues, it wasillustrated that Duffy antigen is

upregulated in earlyrheumatoid arthritis and has a determining role in recruitment of neutrophils to the synovium[32]. In another study by Carsten Minten et al., they demonstrated that Duffy receptorsare upregulated in autoimmune encephalomyelitis, conveying proinflammatory cytokines from luminal to abluminal surfaces of the blood-brain barrier[33]. Furthermore, DARC-positive small vessels, especially alveolar wall capillaries, were associated with inflammatory sites that were marked by interstitial CCR5-positive T-cell and CXCR1-positive leukocyte infiltrates. The study, also, revealed increased expression of Duffy receptors during acute phase of lung rejection[34].

Interestingly, even, the different positive phenotypes of DARC (FY (a+/b-), FYb (a-/b+), FY (a+/b+)) has been corroborated to be determinant in susceptibility of various diseases and, surprisingly, their severity. Based on a study conducted in 2009, Nil Guleret al. concluded that higher ratios of phenotype FY (a+/b+) is seen in patients with multiple myeloma than healthy ones[35]. In another study by Mun Yik Fong et al., they figured out that Plasmodium knowlesi has higher binding affinity for erythrocytes with FY (a+/b+) antigens than those with only FYa antigens[36]. In 2018, it was further demonstrated that patients with FY (a-/b+) phenotype are more susceptible to develop clinical malaria; however, those with FY (a+/b-) phenotype are more likely to be asymptomatic[37]. Despite these, our study provides no significant association between the three different Duffy positive phenotypes and increased risk of developing preeclampsia among the study population. This findingdoes not mean that no association exists between DARC phenotypes and susceptibility to preeclampsia; asthose with Duffy null phenotypes were not included in our study due to the low prevalence of FY(a-/b-)phenotype among Caucasians[38]. Therefore, comparison between the prevalence of preeclamptic toxaemia among them and those with Duffy positive phenotypes has not been investigated in the current research.Further studies are demanded to be designed in this area to investigate possible effect of DARC presence or its absence in preeclampsia pathogenesis. Such analyses should be encouraged in order to delineate the underlying biologic pathways and their disruption in pathologic conditions.

CONCLUSION

Day by day, the underlying pathologic pathways of formerly idiopathic diseases are being discovered. Genetic codeshave been shown to highly affect these pathways, triggering a cascade that ends with the disease entity. However, our article does not support a significant association between different positive phenotypes of DARC and susceptibility to preeclampsia, these studies should be encouraged in order to delineate the underlying biologic pathways and their disruption in pathologic conditions.

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