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Estimation of Natural Autoantibodies in Preeclampsia by ELI-P Complex

Gioulia Romanidou[1,2], Theocharis G Konstantinidis[3*], Konstantia Kantartzi[1], Maria Panopoulou[3], Emmanouil Kontomanolis[4], Stylianos Panagoutsos[1], Ploumis Passadakis[1] and Christina Tsigalou[3]

[1]Department of Nephrology, Democritus University of Thrace, University General Hospital of Alexandroupolis, Dragana Campus, 68 100 Alexandroupolis, Greece

[2]General Hospital "Sismanoglio", Sismanoglou 45, 69133 Komotini, Greece

*[*3]Laboratory of Microbiology, School of Medicine, Democritus University of Thrace, Dragana Campus, 68100 Alexandroupolis, Greece*

[4]Department of Obstetrics and Gynecology, Democritus University of Thrace, University General Hospital of Alexandroupolis, Dragana Campus, 68100 Alexandroupolis, Greece.

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ABSTRACT

Preeclampsia (PE) is one of the most serious complications of pregnancy. Disturbances in immune regulation are one of the most common reasons that negatively influences the gestation process and play an important role in pathogenesis of PE We hypothesize that alteration of serum natural autoantibodies' level, may be associated with PE. Natural autoantibodies were measured by ELI-P complex in maternal sera from preeclamptic subjects in comparison to normal pregnancies. The corresponding peaks of immunoreactivity were selectively affected in approximately 89% of preeclampsia and 12 % control pregnant ($p<0,001$). This study confirms the high level of immunological activation in patients with PE. The presence of autoantibodies implies that autoimmunity might have a causal role in the pathogenesis of PE.

INTRODUCTION

Preeclampsia (PE) is a common obstetric critical disease that affects 8-10 % of pregnancies worldwide [1]. It is a major cause of maternal morbidity and mortality [2]. Predominant clinical manifestation of PE are hypertension, edema, and proteinuria [3,4]. In some cases, the disease can occur without proteinuria [4]. The cardinal risk factors for development of PE have been described as a prior history of preeclampsia, maternal preexisting comorbidities such as hypertension, pre-gestational diabetes, autoimmune disorders such as anti-phospholipid syndrome and systemic lupus erythematosus as well as increasing maternal age beyond 35 and assisted reproductive techniques [5]. Effective and reliable predictive tests for early diagnosis of preeclampsia have not discovered yet [6].

Mechanisms that play role in the pathophysiology of preeclampsia include an irregular placentation and local inflammatory response [7]. The cornerstone role of the placenta in preeclampsia was highlighted in many articles [7-10]. Oxidative stress, hypoxia, endothelial dysfunction and decidual vasculopathy are considered to result in failure of dialogue between trophoblast cells and maternal tissues, and consequently abnormal placentation [8]. Hypoxia leads to upregulation in hypoxia-inducible factor (HIF)-1a and HIF-2 and downregulation of vascular endothelial growth factor (VEGF) via VEGFR-2 promotes endothelial dysfunction [11,12].

It was previously reported that disturbances in immune regulation are one of the most common reasons that negatively influences the gestation process. Phagocytic cells, monocytes and neutrophils play an essential role in the pathogenesis of preeclampsia [13,14]. Interestingly, Gupta et al, show that placent derived factors activated peripheral neutrophils to generate neutrophil extracellular traps (NETs) [15]. NETs comprise a pivotal parameter in PE. NETosis is involved in inflammatory component of placental dysfunction by the increased release of placental micro-debris or by microthrombotic disorders and thromboinflammation [15,16]. In addition, many studies

Corresponding author: Theocharis G Konstantinidis, Laboratory of Microbiology, School of Medicine, Democritus University of Thrace, Dragana Campus, 68100 Alexandroupolis, Greece, Tel: +30-2551352005; E-mail: tkonsta@med.duth.gr

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have reported that genetic factors contributing to inflammatory response in PE [17,18].

At the beginning of the 21st century, the term 'Immunculus' has been proposed by Poletaev and Osipenko for describtio of the global system (network) of constitutively expressed natural autoantibodies (na-Ab) interacting specifically with different self-antigens [19]. In healthy individuals the repertoires of each na-Ab are surprisingly constant and characterized by minimal individual quantitative variations [20].

Our study aims to evaluate the IgG autoantibodies against different autoantigens in the serum of patients with PE by ELI-P complex method and its usefulness and application in daily practice.

MATERIALS AND METHODS

The Study Design

This study was performed at the University General Hospital of Alexandroupolis and Democritus University of Thrace in Alexandroupolis, Greece. The study protocol was approved by the local committee of ethics and deontology in accordance with the Declaration of Helsinki (Ethics Committee identification code: 941).

Study Population

This study included 92 pregnant women persons mean age 32.38±1.59 yrs. All patients were divided into two groups: Preeclampsia n=57, and control n=35. Serum and urine samples were collected on admission to the hospital. The period of sampling was from June 2014 to May 2020.

Biochemical analysis

Biochemical tests were performed by automated biochemical analyzer. To estimate the renal function sCr was measured using an automated biochemical analyzer, and the estimated glomerular filtration rate (e-GFR) was calculated using CKD EPI formula.

ELI -P complex ELISA

Median individual immune reactivity (MIR) and profiles of individual immune reactivity (relative content) of the corresponding autoantibodies were detected and analyzed in the blood serum samples as described previously by Poletaev AB [21]. ELI-P-Complex method is intended for measuring the profiles of specific serum immune reactivity (IR) which depends on a serum content of twelve IgG a-Abs to Chorionic Gonadotropin (hCG), dsDNA, β2-Glycoprotein I, Fc-fragment of IgG (rheumatoid factor), collagen II, insulin, thyroglobulin, proteins of S100 family, Spr-06-antigen of sperm membranes, TrM-03-antigen of platelet membranes, ANCA, KiM-05-antigen of kidney cell membranes. Selective increase in serum immunoreactivity with certain antigens from +10% and above or selective decrease from -15% and below (from the individual average level of the reaction) were considered as abnormal peaks.

RESULTS

The systolic as well as diastolic pressure was increased in PE in a statistically significant manner 160.14±7.6 vs 128.3±7.1, and 92.6±1.4 vs 74.7±7.5, respectively. The characteristics and laboratory findings of the study population are presented in **Table 1**.

Table 1. Clinical and demographic characteristics of study population.

	Preeclampsia; n= 57	Controls; n= 35	P value
Age (years), mean (±SD),	32.38±1.59	29.9±4.3	0.14
Systolic BP, mean (±SD), mm Hg	160.14±7.6	128.3±7.1	<0.001
Diastolic BP, mean (±SD), mm Hg	92.6±1.4	74.7±7.5	<0.001
Gestational age (weeks)	32.01±1.8	38.09±2.7	0.071
Laboratory findings			
WBC (±SD) K/μl	12212.6±3914.2	11237.8±1 477.8	0.58
Hb (±SD) g/dL	11.1±0.91	12.2±0.5	0.3
Platelets (±SD) K/μl	200.1±24.6	231.9±26.9	<0.001
MPV (±SD)	10.02±0.8	8.8±0.82	<0.001
Glucose (±SD) mg/dL	102.1±9.5	95.01±16.3	0.054
eGFR	112.5±12.3	106.3±26.9	0.048
Creatinine mean (±SD) mg/dL	0.6±0.014	0.56±0.005	0.3
Urea mean (±SD) mg/dL	26.3±5.7	19.72±4.04	0.003
SGOT (±SD) U/L	112.8±38.1	16.4±2.3	<0.001
SGPT (±SD) U/L	108.4±48.6	14.3±3.5	<0.001
Uric acid (±SD) mg/dL	6.3±1.8	4.6±1.04	<0.001
CRP (±SD) mg/dL	1.4±1.01	0.67±0.5	0.071

The corresponding peaks of immunoreactivity were selectively affected in approximately 89% of preeclampsia and 12 % control pregnant (p<0,001). More specifically, IgG autoantibodies to chorionic gonadotropin (hCG) were found

to be elevated in 8 (14%) patients of PE group vs. 1 (2.5%), anti-β2-Glycoprotein I a-Abs were decreased in 16 (28,1%) PE patients, while were found to be elevated in 3(5,2%). Antibodies to collagen II were decreased in 38 (66,6%) patients vs. 4 (11,4%) in control groups. Antibodies to insulin, were elevated in 26 (45,6%) vs. 6 (17,1%). Moreover, in our study the increasing level of anti-insulin antibodies were correlated with highest glucose level **(Figure 1)**. Antibodies to proteins of S100 family were increased in 37 (64.9%) vs. 7 (20%). Anti-platelet antibodies, TrM-03-antigen of platelet membranes, were increased in patients with PE, who develop HELP syndrome. We also found that serum level of anti -KiM-05-antigen of kidney cell membranes were inversely associated with preeclampsia.

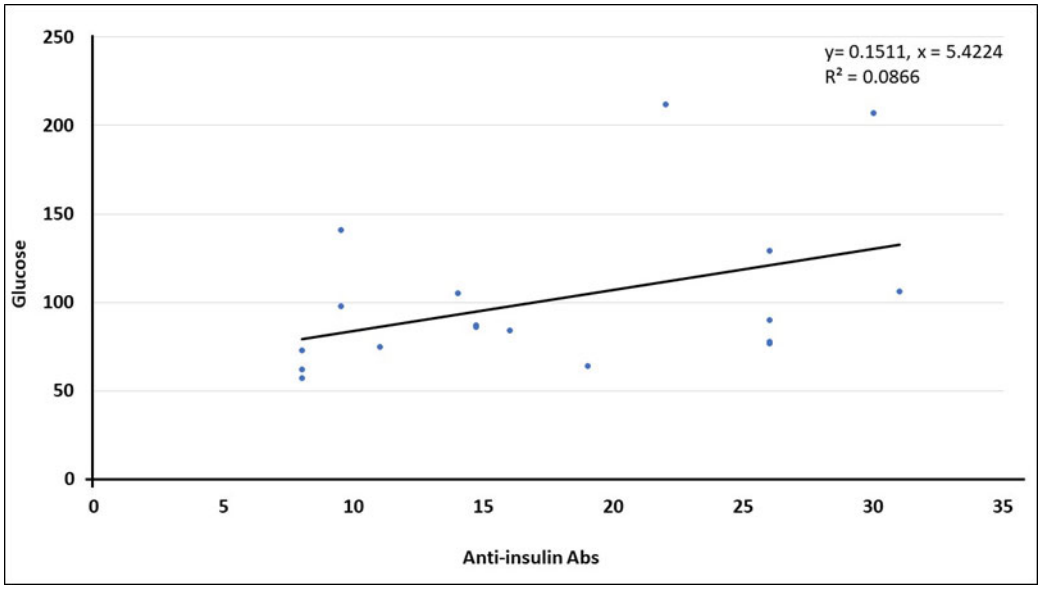

Figure 1. Correlation between anti insulin aAbs and glucose level in PE patients.

DISCUSSION

For a long time, the elevated levels of autoantibodies have been associated exclusively with the pathogenesis-diagnosis of autoimmune diseases. Nevertheless, it has been recognized that the level of autoantibodies can be increased in other diseases, not within the spectrum of autoimmunity, like asthma, stroke, cognitive dysfunction in children and adults etc. [22,23].

We report the laboratory findings of a cohort of 57 patients with PE, from whom 89% have been affected tests for autoantibodies. The diagnosis of PE is based on clinical criteria, while laboratory tests show wide variability within assays, making diagnosis quite difficult.

In this study, we found that the mean individual immune reactivity in PE was significantly higher than in the control subjects. Our results are in line with previously reported data [21,24].

We found that antibodies to ds DNA was inversely associated with preeclampsia. It is worth noting that regarding antibodies to ds DNA it is several contradictory data: in several works, a clear increase in their concentration was noted in patients with PE, while, on the other studies its decrease [24,25].

Antibodies to collagen were decreased in PE group in comparison to controls (38/66,6% vs. 4/11,4%). A possible explanation for this might be that a-Abs cannot be detected because they form complexes with antigens which are in excess in patients with PE. Nikolov [26] report that serum levels of collagen were elevated in early-onset preeclampsia [26]. Antibodies to insulin were increased in 21 (36.8%) patients PE. It is well documented that gestational diabetes mellitus consists of risk factor for develop of PE [27,28]. This may be a potential explanation for the presence of antibodies to insulin in patients with PE. Moreover, in our study the increasing level of anti-insulin antibodies were correlated with highest glucose level **(Figure 1)**.

We also found that serum levels of anti S100 a-Abs were associated with preeclampsia. S100 proteins regulate various cells' signaling pathways. Studies report that increased level of S100 proteins is found to be associated with pregnancy disorders such as preeclampsia or early pregnancy loss. [29,30].

Additionally, serum levels of anti -KiM-05-antigen of kidney cell membranes was inversely associated with preeclampsia. It is well documented that preeclampsia is characterized by kidney damage, and consequence proteinuria. The production of kidney specific antigens may be triggered by kidney damage. Moreover, the new

environment during pregnancy (the process of placentation) triggers physiological changes that modulate kidney function, with intention to control extracellular volume and acid-base balance during the pregnancy. This bidirectional communication between placenta and kidney signifies that changes or dysfunction of one organ influence over the others [31]. In accordance with the above, it is possible that a-Abs cannot be detected because they form complexes with antigens which are in excess in patients with PE.

In conclusion, changes in the production of autoantibodies play an important homeostatic role in various disorders as in preeclampsia. The study of autoantibodies provides optimization of the differential diagnosis of preeclampsia, makes it possible to predict the development of complications in preeclampsia such as kidney damage or hyperinsulinemia, and might significantly reduce maternal and infant morbidity and mortality.

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