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Serum uric acid and inflammation in patients with immune thrombocytopenic purpura: preliminary results

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Abstract. – OBJECTIVE: The purpose of this study was to evaluate the uric acid (UA) and C-reactive protein (CRP) levels in patients with immune thrombocytopenic purpura (ITP).

PATIENTS AND METHODS: Forty patients with newly diagnosed ITP and 40 healthy individuals were enrolled in the study. The patients were divided into two groups; group 1 (n = 40) consisted of patients with ITP, and group 2 (n = 40) consisted of healthy subjects. UA and CRP levels were measured in the blood samples from them.

RESULTS: There were no statistical differences in gender, age and body mass index between two groups ($p > 0.05$ for all). Compared to group 2, group 1 had significantly higher UA levels (p = 0.002), whereas CRP levels were not significantly different ($p > 0.05$). In ITP patients, serum UA and CRP levels significantly correlated with low platelet count (r = –0.362, $p = 0.022$; r = –0.383, $p = 0.015$, respectively); and UA levels significantly correlated with CRP levels (r = 0.436, $p = 0.005$).

CONCLUSIONS: The present study showed that UA levels increased in patients with ITP and negatively correlated with platelet counts. UA levels might be a mediator of inflammation via enhanced production of inflammatory cytokines; they might also be a potential mediator of low platelet count, and could play a pathophysiological role in the development of ITP.

Key Words:
C-reactive protein, Immune thrombocytopenic purpura, Uric acid.

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by the presence of autoantibodies against thrombocyte membrane proteins. The rapid removal of antibody-coated thrombocytes from the circulation by phagocytes in the reticuloendothelial system, especially in the spleen, plays a primary role in the pathogenesis of ITP. Although the etiology of ITP is not definitely known, genetic and environmental factors are considered to have a role in its development. It is well established that platelets are actively involved in inflammation and immune-mediated disorders[1-5].

Uric acid (UA), a product of purine catabolism, was identified in dying cells and enhanced dendritic cell maturation and the CD8-T-cell response. It is a potent mediator of inflammation and a marker of tissue injury[6-11]. Uric acid also stimulates human monocytes to produce pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, which are elevated in the circulation of experimentally-induced hyperuricemic animals[10]. A link between soluble UA and induction of inflammation has also been suggested by previous reports[12,13] where UA has been identified as a signal of danger released in the context of cell death–inducing inflammation, or adaptive immunity.

Although UA has been shown to be a mediator of inflammation via enhanced production of inflammatory cytokines and could serve a pathophysiological role as a local alarm signal that alerts the immune system to cell injury and helps to trigger both innate and adaptive immune responses[14,15], no research study has been performed to evaluate the role of UA in the development of ITP. Therefore, in this study, we aimed to investigate the hypothesis of uric acid acting as a possible pro-inflammatory triggering agent in patients with ITP.

Patients and Methods

Study Design a Patients

This cross-sectional study was conducted at the Hematology Department of Dicle University

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School of Medicine, Diyarbakir, Turkey. Prior to the recruitment of subjects, the study protocol was reviewed and approved by the local Institutional Board, in accordance with the ethical principles for human investigations, and a written informed consent was obtained from all the patients. 40 patients with newly diagnosed ITP and 40 age-gender matched healthy individuals were consecutively recruited for the study.

Patients were divided into two groups: group 1 (n=40) consisted of patients with ITP, and group 2 (n=40) consisted of healthy subjects. The exclusion criteria were as follows: recent acute infectious illness; any evidence of liver, kidney diseases; diabetes mellitus; malignancy; any other inflammatory, or infiltrative disorder; recent use (within 2 weeks) of any systemic drug; regular alcohol use or alcohol use within the previous 48 hours. The serum UA and C-reactive protein (CRP) levels of all ITP patients were analyzed, and blood sample data were also obtained from the healthy subjects.

Baseline Definitions and Measurements

Height and weight were measured according to standardized protocols. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters square (kg/m^2).

Biochemical Analysis

All blood samples were drawn from a large antecubital vein without the interruption of venous flow, using a 19-gauge butterfly needle connected to a plastic syringe. Twenty milliliters of blood were drawn, with the first few milliliters discarded. Ten milliliters were used for baseline routine laboratory tests. UA, CRP, urea, creatinine, aspartate aminotransferase, and alanine aminotransferase levels were measured in the serum samples, and determined by using commercially available assay kits (Roche, Indianapolis, IN, USA) with an auto-analyzer (Roche Cobas Integra 800 auto-analyzer).

Statistical Analysis

All statistical analyses were performed, using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test the normality of data distribution. The data were expressed as arithmetic means and standard deviations. The chi-square test was used to compare the categorical variables between groups. Independent sample *t*-test was used for the comparison of continuous variables between two groups. Pearson's correlation analysis was used to examine the association of demographic and biochemical variables with UA in ITP patients. Two-sided p value < 0.05 was considered to be statistically significant.

Results

The clinical and demographic characteristics of the study groups were presented in Table I. There were no significant differences in gender and age between the control and ITP patients ($p > 0.05$ for all). Compared to control patients, ITP patients had significantly higher levels of UA levels ($p = 0.002$); whereas CRP levels were not significantly different ($p > 0.05$). In ITP patients, serum UA levels and CRP levels were significantly correlat-

Table I. Comparison of the demographic and anthropometric and biochemical characteristics of all patients.

Variables	Group 1 (n = 40)	Group 2 (n = 40)	p
Gender, male/female	8/32	12/28	0.439
Age, years	40.85 ± 17.32	37.55 ± 11.56	0.320
BMI, kg/m^2	28.57 ± 3.73	27.41 ± 3.00	0.132
Urea, mg/dL	33.27 ± 9.56	31.57 ± 7.44	0.378
Creatinine, mg/dL	0.51 ± 0.19	0.45 ± 0.20	0.204
ALT, U/mL	18.23 ± 6.28	20.30 ± 6.30	0.146
AST, U/mL	17.20 ± 7.09	18.70 ± 6.74	0.335
Hemoglobin, mg/dL	12.59 ± 1.45	12.95 ± 1.68	0.313
WBC, /uL	8742 ± 4568	7244 ± 3534	0.105
CRP, mg/dL	1.35 ± 0.86	1.09 ± 0.98	0.221
Platelets, /uL	34281 ± 29548	202475 ± 61871	**< 0.001**
Uric acid, mg/dL	6.76 ± 0.90	6.15 ± 0.77	**0.002**

All measurable values are given as the mean ± standard deviation. BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell; CRP: C-reactive protein.

ed with low platelet count (r = –0.362, $p = 0.022$; r = –0.383, $p = 0.015$, respectively); and UA levels were significantly correlated with CRP levels (r = 0.436, $p = 0.005$) (Figure 1).

Discussion

This is the first study that investigated the serum UA levels in patients with ITP, and the main results were that; (1) UA levels were found to be higher in patients with ITP; and (2) UA levels were significantly correlated with CRP.

Several studies[11,16,17] have investigated the role of increased UA in directly mediating the inflammation via stimulating inflammatory cytokines. A relationship between serum UA level and inflammation has also been shown in clinical studies using various circulating inflammatory markers, such as fibrinogen, monocyte chemoattractant protein-1, interleukin-6, and tumor necrosis factor-α, and CRP[18-20]. Ruggiero et al[21,22] revealed that uric acid was positively associated with IL-6, TNF-α, and CRP, and these authors observed that UA predicted CRP increases. Lyngdoh et al[19] observed that UA was associated positively with IL-6, CRP, and TNF-α and negatively with interleukin-1 beta. These results support the hypothesis that UA is involved in inflammation by triggering the release of inflammatory cytokines[23]. In our study, we found increased UA levels but we also found similar CRP levels in patients with ITP when compared to the controls; and UA levels were found to be positively correlated with CRP levels.

Decreased platelet counts were also observed in the group with higher uricemia levels, and the mechanism(s) by which UA may endanger organ damage is still incompletely understood[24,25]. UA mediates the immune system to cell injury and helps to trigger immune responses[15]. To become immunologically active, it is thought that UA has to undergo a phase change to mono-sodium urate (MSU) crystals. Pure MSU crystals have been shown to augment immune responses. The inflammatory component of these immune responses is caused when urate crystals trigger both inflammasome-dependent and independent pathways to generate the proinflammatory cytokines. Recent studies[8,15] point to a different potential pathophysiological role for UA in alerting the immune system to danger. Shi et al[8] reported that increased UA released from damaged cells during infection enhances the generation of immune responses. In addition, Fontana et al[1] reported interstitial lung disease developing in 3 patients with severe ITP, and the authors proposed that the inflammatory reaction in the lung may develop in acute phases of platelet destruction in ITP. Finally the authors concluded that platelet destruction may have been triggered by the inflammation. As discussed above, UA stimulates inflammation, and this inflammation can cause further tissue injury and contribute to disease, for example infarcts or other injuries[15]. In our study, we found that both UA and CRP levels were correlated with low platelet counts; UA might trigger, though not definitely, the inflammation and immune response resulting in the destruction of the platelets and development of the disease, ITP.

Conclusions

The present study showed that UA levels increased in patients with ITP and negatively cor-

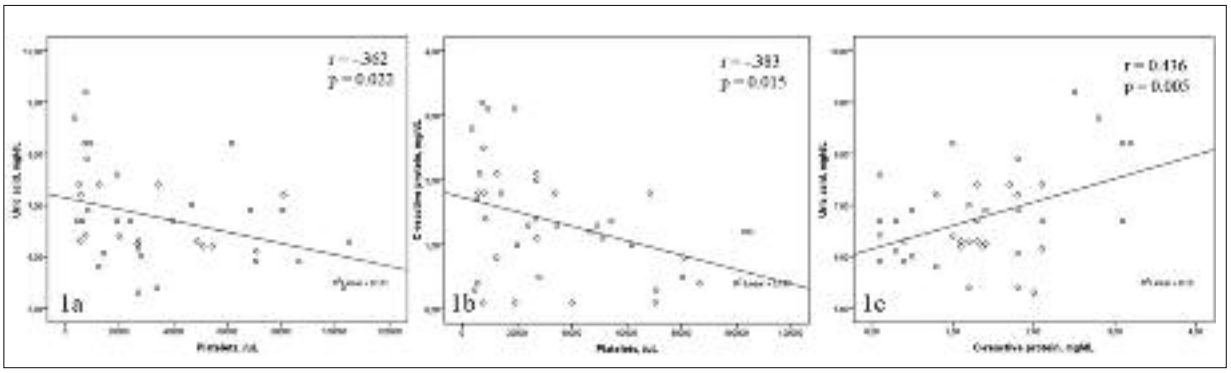

Figure 1. ***1a,*** Graph demonstrating the correlation analysis of uric acid levels and platelet count. ***1b,*** CRP and platelet count. ***1c,*** uric acid and CRP levels.

related with platelet counts. UA levels might be a mediator of inflammation via enhanced production of inflammatory cytokines and a potential mediator of low platelet count, and could serve a pathophysiological role in the development of ITP. In this study, we propose a mechanism through which higher UA concentrations mediate the immune modulation and inflammatory responses by facilitating the development of ITP. More detailed information would be gained by assessing the other inflammatory parameters along with the UA levels; the investigation would perhaps provide deeper insight into the role of the UA levels in patients with ITP, and might add to the value of our manuscript. Therefore, further research is needed to better understand the biological roles of UA, and identify new therapeutic targets in the prevention and treatment of ITP.

Conflict of Interest

All authors declare that there is no conflict of interest or financial support.

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