

Akut ve kronik ürtiker hastalarında platelet belirteçlerinin, c-reaktif protein düzeyleri ve hastalık şiddeti ile karşılaştırılması

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Öz

Bu çalışmada; akut ve kronik ürtikerli hastalarda, platelet belirteçlerini ve C-reaktif protein düzeyleri ölçülmüştür. Ürtiker patogeneğinde plateletlerin rolünü araştırmak amaçlandı. Çalışmaya 18-76 yaş arasında 34 akut ürtiker hastası, 27 kronik ürtiker hastası ve 30 sağlıklı gönüllü alınmıştır. Gruplar arasında demografik veriler açısından anlamlı fark saptanmamıştır. Platelet belirteçlerinden MPV ve PDW değerlerinde akut ürtiker ve kronik ürtiker grubu arasında fark saptanmaz iken, kontrol grubunda bu değerler istatistiksel olarak anlamlı yüksek bulundu ($p<0,001$). Kontrol grubunda CRP değeri istatistiksel olarak anlamlı düşük bulundu ($p:0,008$). Ürtiker patogeneğinde plateletlerin rolünün daha iyi anlaşılması için geniş hasta serilerinde çalışmalara gereksinim vardır.

Anahtar Kelimeler: Ürtiker, platelet, C-reaktif protein

Yayın Bilgisi

Gönderi Tarihi:10.09.2018

Kabul Tarihi:17.10.2018

Online Yayın Tarihi:31.03.2018

DOI: 10.26453/otjhs.458544

Sorumlu Yazar

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Comparison of platelet markers with c-reactive protein levels and disease severity at patients with acute and chronic urticaria

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Abstract

In this study; Platelet markers and C-reactive protein levels were measured in patients with acute and chronic urticaria. The aim of this study was to investigate the role of platelets in the pathogenesis of urticaria. The study included 34 acute urticaria patients, 27 chronic urticaria patients and 30 healthy volunteers between the ages of 18-76. There was no significant difference between the groups in terms of demographic data. MPV and PDW values of platelet markers were not significantly different between acute urticaria and chronic urticaria group ($p<0.001$). CRP values were significantly lower in the control group ($p:0.008$). In order to better understand the role of platelets in the pathogenesis of urticaria, large series of patients are needed.

Keywords: Urticaria, platelets, C-reactive protein

Article Info

Received:10.09.2018

Accepted:17.10.2018

Online Published:31.03.2018

DOI: 10.26453/otjhs.458544

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INTRODUCTION

Urticaria is a skin disease characterized by erythematous, edematous, itchy, self-disappearing urticaria lesions. It is the most common skin disease and the most frequent cause of admissions to the emergency department. The rate of encountering urticaria in a person's life is 10-25%. There are various classifications of urticaria. The most common classification method is according to the duration of the disease. The disease with recurrent lesions lasting less than six weeks is defined as acute urticaria. If the disease lasts longer than 6 weeks it is called chronic urticaria.^{1,2} Infections and medications are the main causes of acute urticaria in adults. In childhood, whereas the most frequent cause are infections, food allergies (especially cow's milk) are seen more frequently than adults.³ The etiological causes of chronic urticaria have been reported as acute and chronic infections, drug reactions, and autoimmunity, it is usually defined as idiopathic or unrecognized.⁴ Many studies have been conducted to elucidate these diseases in which immune-to-inflammatory responses play a role. While the number of platelets increases during the inflammation, their volume tends to increase or decrease.⁵

The role of platelets in immunological and inflammatory responses in severe inflammatory diseases, in some diseases such as asthma, arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, familial Mediterranean fever, rheumatoid arthritis, acute rheumatic fever,

and cystic fibrosis and chronic autoimmune urticaria has been shown.⁵⁻¹⁰ However, in a small number of previous studies, MPV and C-reactive protein (CRP) were measured in chronic autoimmune urticaria and control groups and correlation with disease severity was assessed and inconsistent results were reported.^{7,11,12} The aim of this study is to assess the platelet markers that can be measured in the routine hemogram in acute urticaria patients, which was not performed in previous studies, in order to evaluate the correlation with disease severity in both acute and chronic urticaria patients and to compare these values separately with healthy control group, in order to assess any relationship.

MATERIAL AND METHODS

Ethical Approval for the study was obtained from the local ethics committee of Inonu University Medical Faculty. Informed consent was obtained from the patients.

52 patients were included in the study. Who admitted to the Skin and Venereal Diseases Polyclinic of Inonu University Medical Faculty, who were diagnosed with acute or chronic urticaria between and 26 healthy volunteers, between the ages of 18 and 76, were enrolled in the study. First, the patients' anamnesis were recorded and physical examinations were performed. During anamnesis, the patients were asked whether they had ingested any suspicious foods, medicines, inhalants, contacted substances,

physical agents, whether they had atopic diathesis, infectious disease story, tooth decay, psychological stress and systemic diseases that could be the cause of illness urticaria. Patients with systemic disease other than urticarial were not included in the study. In acute urticaria patients, only complete blood counts and CRP tests were performed. In chronic urticaria patient's routine laboratory tests were performed for defining the causes. Complete blood count, sedimentation, blood biochemistry, anti-nuclear antibody, infection panel (HBsAg, antiHBs, antiHCV, throat culture, faecal parasite tests, complete urine analysis and urine culture) were evaluated. Patients' history and / or provocation tests (skin drawing for dermatographics) were done to exclude physical urticaria. When all other causes were excluded due to the patient's history and extensive laboratory tests, patients with residual chronic urticaria were included in the study.

Most of the patients included in the study has used at least one antihistamine before and did not benefit from treatment. None of the patients had received immunosuppressive therapy previously and had no known thyroid disease or autoimmune disease. In addition, additional problems such as infection, inflammatory diseases, and malignancy, which may be associated with elevated serum CRP levels, were questioned in patients and control group. Patients with such an additional condition were excluded from the study. The patients' age, gender, duration of

illness, angioedema was recorded. The urticaria activity scores of the patients were calculated. Serum CRP and complete blood counts were performed simultaneously. Autologous serum skin test (ASST) was applied to the patients with chronic urticaria when urticaria was active. The control group included healthy volunteers who did not take any medication during the last three months, did not have urticarial vasculitis, dyslipidemia, obesity ($BMI \geq 25$), cardiovascular disease, hypertension, deep vein thrombosis, hepatic and renal disease, malignancy, or inflammatory cutaneous diseases. Those who did not meet these criteria were not included in the study.

Evaluation of Urticaria Activity

The urticaria activity scoring system recommended in the GA2LEN guideline was used to determine the severity of the disease. Urticaria activity scores (UAS) are the sum of the number of exanthema score and the severity of the itch score. The total daily score is between 0 and 6. The UAS at the time of admission for all patients were calculated.

Statistical analysis

The statistical analyses of the study data were performed by using SPSS for Windows version 17.0 software. Quantitative data were expressed as mean, standard deviation (SD), and qualitative data as number and percentage (%). For statistical analyzes, compliance with normal distribution of all quantitative variables was tested by the Shapiro Wilk test. Kruskal Wallis Variance

Analysis, Conover test and Mann Whitney U test were used for the comparison of the non-normally distributed variables. The qualitative data were compared by using Pearson and Fisher's exact Chi square test. Statistical significance level was accepted as $p < 0,05$.

RESULTS

The number of patients in the study group and control group was 91, 36 of them were male and 55 were female. The acute urticaria group included 34 patients; 16 of them were male and 18 were female. The chronic urticaria group included 27 patients; 7 of them were male and 20 were female. The control group included 30 persons, 13 of them were male and 17 were female (Table 1). Age and gender characteristics were found to be normally distributed.

The mean age of the acute urticaria group was $36,58 \pm 13,7$ (18-66), the mean age of the chronic urticaria group was $39,4 \pm 15,9$ (18-76) and the mean age of the control group was $33,2 \pm 10,8$ (Table 2).

Laboratory findings including mean platelet volume (MPV) (fl), C-reactive protein (CRP) (mg/dl), platelet distribution width (PDW) values, platelet counts ($\times 10^9/L$) and demographic characteristics including age and gender of the patients in the study groups and the healthy controls were compared. The number of male and female patients in the acute urticaria group was approximately equal, whereas the number of

female patients in the chronic urticaria group was significantly higher than the male patients (K/E:20/7). There was no significant difference between the groups in terms of the mean age. Average MPV value was $7,89 \pm 0,5$ in acute urticaria group and $7,90 \pm 1,1$ in chronic urticaria group. There was no significant difference between the groups. However, the average MPV value of the healthy controls, who met certain criteria for inclusion, was $10,1 \pm 1,09$ and statistically different from the other two groups ($p < 0,0001$). Average PDW value was $16,52 \pm 0,5$ in the acute urticaria group and $16,21 \pm 1,8$ in the chronic urticaria group; there was no significant difference. The average PDW value of the control group was $12,80 \pm 2,3$ and statistically significantly different from the other two groups ($p < 0,0001$). The mean platelet counts were $276,2 \pm 63,7$, $294,4 \pm 132,6$ and $280 \pm 59,2$ in acute urticaria, chronic urticaria and control groups, respectively; there was no statistically significant difference ($p = 0,794$). Average CRP value was $0,73 \pm 0,8$ in acute urticaria group and $0,76 \pm 0,7$ in chronic urticaria group, and $0,50 \pm 0,6$ in the control group. The difference between the control group and the study groups was significantly different ($p = 0,0080$). The mean UAS scores of patients with acute urticaria and chronic urticaria were $2,7 \pm 0,9$ and $2,7 \pm 1,06$, respectively, and there was no significant difference (Table 3).

The p value for the average MPV, PDW, and CRP values of the three groups were found to be $p < 0,05$ and the Conover test was used to

determine the difference group. The difference group was determined to be the control group. According to this finding, there was no significant difference between acute and chronic urticaria groups in terms of MPV, PDW, and CRP values but there was a significant difference between both groups and the control group.

We found that 14 of the autologous serum skin tests performed on the chronic urticaria group were negative (51,9) and 13 were positive (48,1). 10 (50%) of the positive were female, 3 were male (42,9); 10 of the negative were female and 4 (57,1%) were male (Table 4).

In the chronic urticaria group the average MPV, PDW, platelet count, CRP and UAS values were compared between ASST-negative and ASST-positive patients. The average MPV values of ASST negative and ASST positive patients in chronic urticaria patients were $7,69\pm 0,9$ and $8,2\pm 1,39$, respectively ($p=0,259$). The average PDW values were $15,8\pm 2,4$ and $16,6\pm 0,7$ ($p=0,519$). The average platelet counts were $304,4\pm 178,9$ and $283,6\pm 56$ ($p=0,616$). The average CRP values were $0,6\pm 0,7$ and $0,8\pm 0,7$ ($p=0,128$). The average UAS were $2,3\pm 1$ and $3,07\pm 0,8$ ($p=0,105$). There was no significant difference between the groups in terms of these values (Table 5).

DISCUSSION

Urticaria is a disease of erythematous, edematous papules, the main responsible cells are the mast cells, basophils and histamine released from

them. Apart from histamine, active mast cells produce urticarial lesions with nerve stimulation, vasodilatation, and extravasation of the plasma due to the release of platelet activating factor and other mediators such as cytokines. Although all pathways that stimulate mast cells in urticaria are not completely known, it may occur through IgE mediated or very different pathways.⁷ However, in recent years there have been many publications showing that activation of coagulation system with production of thrombin in chronic urticaria increases coagulation tissue factor expression in eosinophils. Asero et al. reported that activation of the coagulation cascade is a potential mechanism of increasing chronic inflammation, but probably not the trigger of the disease.¹²

Some studies have shown that platelet volume directly correlates with platelet function. MPV value is included in complete blood count which we see almost in every patient during our daily practice. Previously, studies regarding high levels of MPV detected in acute stroke, myocardial infections, atherosclerosis, arterial hypertension and diabetes have been published. Large platelets are an in vivo indicator for the activation of adjacent platelet activation, coagulation cascade. Magen et al. in their study on patients with chronic urticaria, reported increased platelet volume and CRP in patients with positive autologous serum test.¹¹ In a different study, there was no significant difference between the number of platelets, MPW and PDW between the chronic urticaria group and the control group, whereas the

serum CRP level was significantly higher in the chronic urticaria group.¹³ Isiksaçan and colleagues examined the risk of vascular thrombosis and homeostatic status of chronic urticaria patients, platelet aggregation and coagulation parameters, and compared them with healthy controls.¹⁴ In chronic urticaria patients, the D-dimer was significantly higher than the healthy controls, the MPV was significantly lower, and the PDW and platelet counts were not significantly different between the two groups. There was no significant difference in prothrombin time, active partial thromboplastin time, and fibrinogen levels among the groups. Akelma and his colleagues conducted a similar study on 40 children who were diagnosed with CSU according to the current guide during one year. They compared the MPV and CRP levels of the healthy control group and the patient group in terms of age, sex and number. MPV (fl) levels were significantly lower in the chronic urticaria group than in healthy controls. The MPV of the chronic urticaria group was $7,42\pm 0,77$, while it was $7,89\pm 0,65$ in the control group. Platelet counts and CRP measurements were significantly higher in the patient group than in the control group ($p=0,008$). This significant difference supported the view suggesting chronic inflammation in these patients.⁵ In this study, MPV was found to be significantly lower in the patient group than in healthy controls. This result was consistent with previous studies showing that MPV levels were lower in children with various

inflammatory diseases, though opposed to adult studies.¹⁵

All studies on platelet markers and homeostatic status have been performed in patients with chronic urticaria. In our study, we studied on acute urticaria group, chronic urticaria group and healthy controls to determine the importance of platelets and inflammation in the pathophysiology of urticaria regardless of urticaria type. The average MPV values were approximated to each other in the acute and chronic urticaria groups, and the difference between them was not significant. However the mean MPV value of the control group selected according to certain criteria was $10,1\pm 1,09$. There were statistically significant differences between two groups ($p<0,0001$). The average PDW values were $16,52\pm 0,5$ and $16,21\pm 1,8$ in the acute and chronic urticaria groups, respectively and there was no significant difference between them. The average PDW value of the control group was $12,80\pm 2,3$ and statistically significantly higher than the other two groups ($p<0,0001$). The averages of platelet counts were not significantly different between acute urticaria, chronic urticaria and control groups ($p=0,794$). Finally, CRP values were significantly higher in the acute and chronic urticaria groups than in the control group ($p=0,0080$).

The average urticaria activity scores of the acute urticaria and chronic urticaria patients at the time of admission were $2,7\pm 0,9$ and $2,7\pm 1,06$, respectively; there was no significant difference

between them. In addition, there was no significant difference in platelet counts, MPV, PDW, and CRP values between the acute urticaria and chronic urticaria groups when blood tests were taken. This findings support the idea, also shown in the study of Asero et. al., that the coagulation system is activated regardless of the subset of the disease and does not play a key role.¹² MPV and PDW are simple, practical indicators of coagulation activation.¹⁶ According to this information, there was no significant difference in coagulation cascade activation between acute and chronic urticaria patients. In our study, the average MPV values were close to each other between acute and chronic urticaria groups, whereas it was significantly higher in the healthy control group. This result contradicts with all other studies except the study of Işıksaçan and Akelma.^{5,14} Our results, being only compatible with two studies from our country, suggest the role of genetic factors and similar laboratory techniques may also affect the results.

We performed ASST in chronic urticaria patients and classified as positive and negative. The MPV, PDW, platelet count, CRP and UAS values of ASST-positive and OSDT-negative patients were compared in chronic urticaria patients group. There was no statistically significant difference between the groups in terms of these values. This findings support the idea, also shown in the study of Asero et. al., that the coagulation system is activated regardless of the subset of the disease and does not play a key role.¹² On the other hand,

Chandrashekar and his colleagues compared hematologic platelet markers in ASST positive and negative chronic urticaria patients and found that only MPV was significantly higher in the ASST positive group and there was no significant difference between the other values.¹³

There is a need for further studies to understand whether the differences of platelet counts, platelet markers such as PDW and MPV, and CRP levels in acute and chronic urticaria patients are epiphenomenal or pathogenetically related conditions. As a result, the exact etiology and pathogenetic mechanisms of chronic urticaria is still unclear. However, most authors agree that the disease should be regarded as a chronic inflammatory or autoimmune condition.

CONCLUSION

More studies with larger patient groups are required in order to comprehend the role and significance of platelets at pathogenesis of urticaria.

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Table 1. Distribution of Gender of the patients and healthy controls groups.

	Male	Female	Total
Acute urticaria	16 (% 47,1)	18 (%52,9)	34 (%100)
Chronic urticaria	7 (%25,9)	20 (% 74,1)	27 (%100)
Control group	13 (% 43,3)	17 (% 56,7)	30 (%100)
Total	36 (% 39,6)	55 (% 60,4)	91 (%100)

Table 2. Age range and average age of study groups and healthy control groups.

	Acute urticaria	Chronic urticaria	Control group
Age range	18-66	18-76	18-53
Mean ± SD	36,58 ± 13,7	39,4 ± 15,9	33,2 ± 10,8

Table 3. Comparison of demographic characteristics, laboratory findings and disease severity scores of the groups.

Variables	Acute urticaria n:34	Chronic urticaria n:27	Control n:30	p
Gender, woman (n%)	18 (%52,9)	20 (%74,1)	17 (% 56,7)	0,215
Age	36,5±13,7	39,4±15,9	33,2±10,8	0,357
MPV (fl)	7,89±0,5	7,90±1,1	10,1±1,09	<0,0001*
PDW (%)	16,52±0,5	16,21±1,8	12,80±2,3	<0,0001*
Number of Platelets (x10 ⁹ /L)	276,2±63,7	294,4±132,6	280±59,2	0,794
CRP (mg/dl)	0,73±0,8	0,76±0,7	0,50±0,6	0,008*
Urticaria Activity Score	2,7±0,9	2,7±1,06		0,879

Table 4. Distribution of ASST according to gender in urticaria group.

ASST	Female	Male
Positive	10 (%50)	3 (%42,9)
Negative	10 (%50)	4 (%57,1)

Table 5. Comparison of laboratory values and urticaria activity score of ASST-negative and ASST-positive patients in the chronic urticaria group.

Variable	ASST- negative (n:14)	ASST- positive (n:13)	p
MPV (fl)	7,69±0,9	8,2±1,39	0,259
PDW (%)	15,8±2,4	16,6±0,7	0,519
Number of Platelets (x10 ⁹ /L)	304,4±178,9	283,6±56	0,616
CRP (mg/dl)	0,6±0,7	0,8±0,7	0,128
Urticaria Activity Score	2,3±1,1	3,07±0,8	0,105