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The Correlation between Markers with the Acute Exacerbation and Severity of the Illness in Patients with Acute Urticaria and Angioedema

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Abstract

Urticaria and angioedema are among the commonly encountered clinical conditions in the emergency department (ED). The severity of these conditions ranges from a simple rash to life threatening uvular edema. Recently, several studies on determining the relationship between the coagulation and inflammation markers with the acute exacerbation and severity especially on chronic urticaria patients have been published. Studies in the literature were primarily focused on patients with chronic urticaria and there appears to be no study on evaluating the level of those markers in patients with acute urticaria or angioedema. We aimed to evaluate the correlation between the coagulation and inflammatory markers with the acute exacerbation and severity of illness in patients presenting to our ED with acute urticaria or angioedema.

Keywords: Acute urticaria; Angioedema; D-dimer; Fibrinogen; MicroCRP

Introduction

Urticaria and angioedema are among the commonly encountered clinical conditions in the emergency department (ED). The severity of these conditions ranges from a simple rash to life threatening uvular edema [1]. Recently, several studies on determining the relationship between the coagulation and inflammation markers with the acute exacerbation and severity especially on chronic urticaria patients have been published. Studies in the literature were primarily focused on patients with chronic urticaria and there appears to be no study on evaluating the level of those markers in patients with acute urticaria or angioedema. We aimed to evaluate the correlation between the coagulation and inflammatory markers with the acute exacerbation and severity of illness in patients presenting to our ED with acute urticaria or angioedema.

Methods

This prospective study was undertaken with patients presenting to the ED of Ankara Training and Research Hospital with acute urticaria or angioedema between May 1st and September 30th of 2010. Permission for the study was obtained from the Ethical Board of the Ankara Training and Research Hospital.

As part of the study, the vital signs, findings from physical examinations, the history and number of previous urticaria or angioedema attacks were recorded in standard study forms. In patients for which acute urticaria or angioedema were diagnosed after the initial anamnesis and physical examination, an intravenous line was started and blood samples for microCRP, fibrinogen and D-dimer were collected in 4 ml citrated and 2 ml biochemistry tubes. The microCRP levels were measured using an *Afinion AS100* device; the fibrinogen and D-dimer values were measured using a Beckman Coulter ACL TOP device. All the patients received initial standard therapy that included intravenous administration of 1 mg/kg of *methylprednisolone*, 50 mg of diphenhydramine, as well as subcutaneous administration of 0.3 to 0.5 mg of 1:1.000 adrenaline for patients with mild angioedema who did not have signs of circulatory compromise. For patients with moderate-to-severe angioedema or acute urticaria with signs of shock 0.3 to 0.5 mg of 1:10.000 adrenaline was administered intravenously.

Assessment of the disease activity of acute urticaria

The disease activity was evaluated according to the chronic urticaria disease activity form that comprises the three levels of severity shown below:

1–10 small (<3 cm in diameter) rash = Grade 1 (slight)

10–50 small wheals or 1–10 large rash = Grade 2 (moderate)

>50 small wheals or >10 large rash = Grade 3 (severe)

Statistical analysis

The statistical analysis was performed using SPSS v16.0. Relationship between categorical variables have been analyzed by Fisher's Exact Test when minimum expected values were less than 5 in 2x2 tables, by Yate's Continuity Test when the minimum expected values were between 5 and 25, and by Pearson Chi-Square Test when the expected values were more than 25. On 2x3 tables, Pearson Chi-Square Test was used when less than 20% of the cells had expected values less than 5. p values were not evaluated when more than 20% of the cells had expected values less than 5. A p-value of <0.05 was considered significant.

Results

During the study period, 253 patients were observed to have been diagnosed either with acute urticaria or angioedema. Of the 202 accepted to be included in the study 92.6% (n=187) had acute urticaria and 7.4% (n=15) had angioedema. The average age of the patients was 41.4 ± 15.4 (mean ± SD). Of all the study patients, 37.6% (n=76) were male and 62.4% (n= 126) were female.

Of the patients with acute urticaria 69.0% (n=129) and 73.3% (n=11) of the patients with angioedema reported no previous history of these complaints. However, 31.0% (n= 58) of the patients with acute urticaria and 26.7% (n=4) of the patients with angioedema stated that they had previously visited an ED with similar complaints more than twice (Figure 1).

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The cut-off value for D-dimer in our laboratory was determined as 253 ng/ml. The average D-dimer value for both groups of patient was 346.97 ± 88.96. The cut-off value for fibrinogen was determined as 500 mg/dl and the average for both patient groups was found to be 550.80 ± 782.37. The cut-off value for microCRP was 0.80 mg/dl and the average for both patient groups was found to be 1.05 ± 1.77. The numbers and frequencies of the patients, whose marker levels in their blood were above the cut-off values are given in the following table (Table 1).

The D-dimer and microCRP levels were both above their respective cut-off values in patients with acute urticaria and this was found to be statistically significant (p<0.001 for D-dimer, p=0.007 for microCRP). No such difference was noted for fibrinogen (p=1.00). We did not observe high levels of D-dimer, fibrinogen and microCRP in any of the patients with angioedema (Figure 2).

No statistically significant difference was found between the patients with or without previous history of acute urticaria or angioedema and elevation in the levels of the three markers (Figure 3).

Upon examination of the correlation coefficients between the severity of rashes and the markers, the highest level of correlation was observed in the D-dimer (r=0.87), whereas the lowest level of correlation was noted in fibrinogen (r=0.213). The correlation level for microCRP was also low (r=0.347). The D-dimer values were different for all three levels of severity of rashes. The D-dimer values for patients at Grade 3 level were higher than those of Grade 1 and Grade 2 patients. The fibrinogen values, on the other hand, were within normal limits in all grades of patients. The microCRP values were also within normal limits and all the patients except for some of the Grade 3 patients in which those values were higher. However, this difference was not statistically significant (Figure 4).

Discussion

Urticaria is a common skin reaction. About 15 to 20% of the population is believed to suffer an urticaria attack at one point in their lifetime [2]. The clinical course of urticaria varies in duration, activity, morphology of lesions and histopathologic structures. Typical lesions are seen as pruritic papules and plaques at the skin surface. The main cause of the itchy rash is the release of mediators such as histamine (the main cause of pruritus), proteases, interleukin-1 and tumor necrosis factor-alpha from dermal mast cells [3]. The majority of attacks are resolved spontaneously within 24-hours of the appearance of the rash. The size of the lesions range from several millimeters to several centimeters and usually various sizes of lesions are present together.

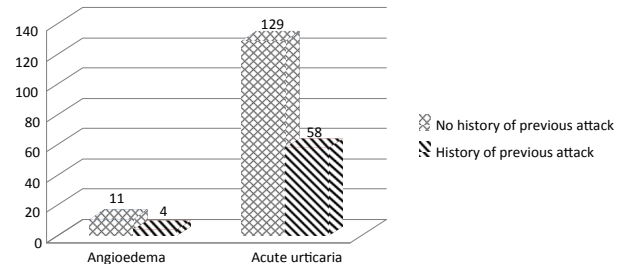

Figure 1: History of attacks in patients with acute urticaria and angioedema.

	N	%
D-dimer > 253	131	64.9
MicroCRP > 0.8	57	28.2
Fibrinojen > 500	7	3.5

Table 1: The blood D-dimer, fibrinojen and microCRP levels of the patients.

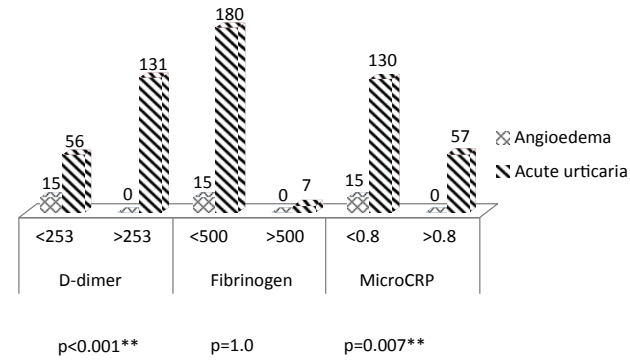

Figure 2: D-dimer, fibrinogen and microCRP levels in patients with acute urticaria and angioedema.

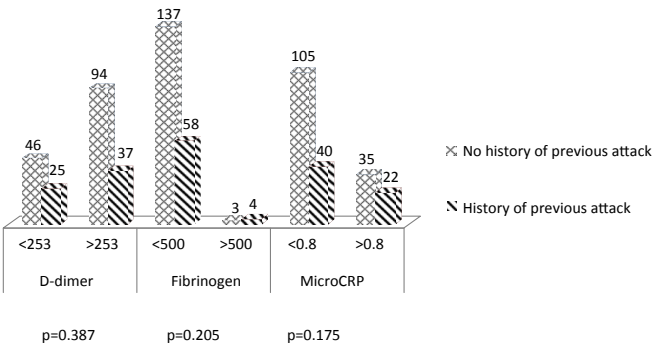

Figure 3: History of previous attack and levels of D-dimer- fibrinogen and microCRP.

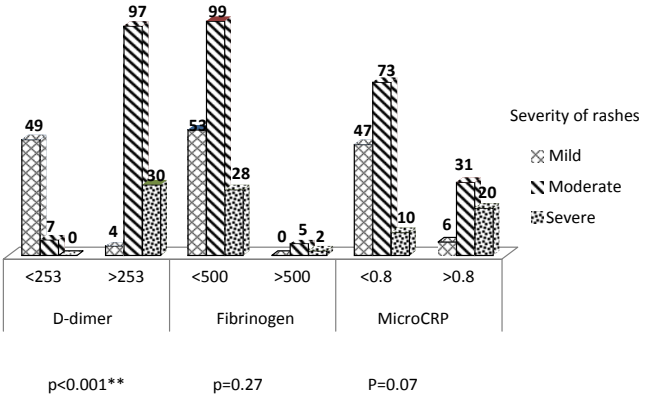

Figure 4: Relationship between the severity of rashes and the levels of D-dimer, fibrinogen and microCRP.

The size and the spread of the lesions are two of the clinical parameters used in determining the severity of the illness. We were unable to find any scoring system to determine the severity of acute attacks therefore, in our study we used the chronic urticaria activity score, which is widely used in literature in evaluation of patients with urticaria [2].

Normal blood flow is regulated by maintaining the delicate balance between coagulation, anticoagulation and fibrinolytic systems. This hemostatic balance prevents both bleeding and clot formation. The formation of plugs by thrombocytes at the site of vascular injury is called primary hemostasis, whereas secondary hemostasis is the formation

of fibrin clots by activated coagulation cascade [4]. The traditional coagulation cascade has two pathways: extrinsic and intrinsic. The extrinsic pathway, which is thought to play a more important role in initiating hemostasis, starts with the release of tissue factors [5,6]. Factor X is activated at the end of these pathways, resulting in the formation of thrombin [7]. Thrombin then activates fibrinogen and fibrin stabilized by Factor VIII is formed. Fibrinolysis is caused after the lysis of fibrin by plasmin. Fibrin degradation products and D-dimer are produced after the breakdown of fibrin [8].

Several studies focusing on the relationship between the coagulation and inflammation markers with the acute exacerbation and severity of chronic urticaria have been conducted in recent years. In 2008, Asero et al. evaluated the correlation of chronic urticaria and coagulation markers finding that plasma prothrombin fragments 1 and 2 and D-dimer were higher in urticaria patients compared to the control group, thus, showing a relationship to the severity of the illness in patients with chronic urticaria [9]. Similarly, we have found that the D-dimer was closely related to the activation of urticaria and was found to be significantly higher in Grade 3 patients. In general, coagulation and inflammation are closely related [10]. CRP, a member of pentraxin family, is an acute-phase protein produced in response to inflammatory cytokines [11]. Along with producing cytokines, CRP also has effects on the vascular system during inflammatory response. It activates the complementary system and increases the production of adhesive molecules, which in turn assist the adherence of white blood cells to blood vessels and move it out of the vascular structures [12]. CRP is synthesized in the liver by interleukin-6 (IL-6). Kasperska-Zajac et al. reported in 2007, that patients with chronic urticaria showed higher levels of IL-6 than healthy controls [13]. Fuji et al., found that IL-6 and CRP levels were high in patients with severe acute urticaria [14]. We found that of the 202 patients in our study, 57 (28.7%) had a higher microCRP level than the cut-off value. This result is similar to the value of CRP level at 23%, found by Takahagi et al. in their study of patients with chronic urticaria [15]. In the same study, the authors also showed that not only the CRP, but also the high level of fibrin degradation products and D-dimer were related to the severity and activity of urticaria.

We did not observe a high level of D-dimer, fibrinogen and CRP in our patients with angioedema. However, Takahagi et al., found a high level of D-dimer and CRP in some of their angioedema patients in their study [15]. Similarly, in a study performed by Cugno et al., found an increased level of protrombin fragments and D-dimer in patients with angioedema that had developed due to C1 inhibitor deficiency [16]. Even though the use of these markers is recommended in the differential diagnosis of patients presenting in ED with abdominal pain of unknown origin, we did not find increased level of any of these markers in our 15 angioedema patients, four of which had a previous history of angioedema.

Conclusion

We found D-dimer and microCRP to be two valuable markers that can be used in determining the severity of acute urticaria. However, further investigations are needed to determine the usability of D-dimer, microCRP and fibrinogen in determining the severity and exacerbation of angioedema in patients suffering from this condition.

Conflict of Interest

The authors declare that there is no actual or potential conflict of interest.

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