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Original Research Article

Correlation between disease activity and markers of coagulation cascade in patients of chronic spontaneous urticaria: a hospital based cross-sectional study

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ABSTRACT

Background: Both extrinsic as well as intrinsic coagulation cascade are involved in the pathogenesis of Chronic spontaneous urticaria. This study was done to correlate the disease activity and markers of coagulation cascade in patients of CSU.
Methods: A hospital-based, cross-sectional, descriptive study was carried out in 100 patients of chronic urticaria. Baseline D-Dimer, prothrombin time, activated partial thromboplastin time was performed. Disease activity was assessed using Urticaria activity score over 7 days.
Results: Of total 100 patients, d-dimer was raised in 72 (72%) patients. Correlation between D-dimer and UAS-7 days showed significant covariance between D-dimer and UAS-7 ($p<0.001$, $r=0.93$). Prothrombin time was raised in 55 (55%) patients. Significant correlation was found between PT and UAS-7 ($p<0.001$, $r=0.76$). Raised APTT was observed in 61(61%) patients. Correlation between APTT and UAS-7 showed that there was a significant covariance between APTT and UAS-7 ($p<0.001$, $r=0.59$).
Conclusions: A significant correlation between markers of coagulation cascade and the disease activity in patients of CSU was seen. These markers can help predict the disease severity and possibly monitor therapeutic response.

Keywords: Coagulation cascade, Extrinsic coagulation pathway, Intrinsic coagulation pathway, d-Dimer, Activated partial thromboplastin time, Prothrombin time, Urticaria activity score

INTRODUCTION

Chronic urticaria is defined as daily appearance of wheals lasting for >6 weeks. It may be spontaneous or inducible. Chronic spontaneous urticaria (CSU) refers to recurrent urticaria with no specific cause or trigger while chronic inducible urticaria is triggered by a well-defined eliciting factor such as pressure, temperature and vibration. Prevalence of chronic urticaria is estimated to be anywhere from 0.5 to 5% in the general population but exact prevalence is not truly known. The incidence is thought to fall around 1.4% annually.[1] It affects patients aged between 20-40 (mean 33 years) years of age and affects women more often than men.[2,3] Although there are several predisposing factors in the pathogenesis of the disease such as food allergies, emotional disturbances, inhalants, drugs, foods, systemic diseases and chronic bacterial, viral and parasitic infections.[4,5] However, a trigger may not be found in a vast majority of patients even after extensive investigations. Recent studies have shown that CSU is a result of an interplay between autoimmunity, inflammation, auto-allergy and coagulation.[6]

Autoimmunity has been implicated in approximately 30-50% of such patients of chronic spontaneous urticaria. Patients with CSU show a positive wheal and flare reaction to intradermal injections of autologous serum, called the autologous serum skin test.[7] In approximately one-third of these patients, IgG autoantibodies against α subunit of high affinity IgE receptor (FcεRI) are present on both mast cells and basophils while 5-10% patients show membrane bound IgE autoantibodies.[7,8] Mast cells and basophils are activated after adjacent FcεRI receptors are cross-linked by these antibodies. This causes release of histamine and other pro-inflammatory mediators from mast cells with the subsequent development of urticarial wheals.[9] Autoimmune theory is further supported by the association of CSU with other autoimmune diseases such as autoimmune thyroiditis.[10] Inflammation is also involved in the pathogenesis of CSU as evidenced by the increase in several inflammatory markers such as C-reactive protein, interleukin-6, matrix metalloproteinase, TNF-alpha and eosinophilic cationic protein, which correlate with urticaria activity.[11-13]

The role of coagulation system in the pathogenesis of CSU is supported by many lines of evidence. The observation that autologous plasma when injected intradermally shows wheal and flare in up to 90% cases of CSU in contrast to 50% positivity with autologous serum, suggested the role of clotting factors in the pathogenesis of urticaria, as autoantibodies are present in equal quantities in both serum and plasma.[14] Specific studies show the role of both extrinsic and intrinsic cascade of coagulation in the pathogenesis of CSU. The role of the extrinsic pathway of coagulation cascade has been suggested by the hyperexpression of tissue factor by eosinophils present in the inflammatory infiltrate.[15,16] This in turn leads to the generation of thrombin and fibrin degradation products such as d-dimer.

Thrombin increases the vascular permeability and plasma extravasation followed by degranulation of mast cells, and thereby causes urticaria.[17] Prothrombin time, which measures extrinsic arm of coagulation cascade and activated partial thromboplastin time, which measures intrinsic arm of coagulation cascade have been shown to be elevated in recent studies on CSU patients.[18] The increase in d-dimer, marker of fibrinolysis, is associated with disease severity.[19] This is evidenced by the poor response to usual doses of antihistamines in patients with elevated d-dimer.[20] It remains to be seen if the severity of urticaria correlates with markers of both intrinsic and extrinsic pathway of coagulation. Hence, we performed a study to elucidate the correlation between disease activity and markers of coagulation cascade in patients of chronic urticaria. This will help the clinicians in deciding the treatment modalities for the patient.

Objectives

The objective was to was to correlate the disease activity and markers of coagulation cascade in patients of CSU.

METHODS

Study type, duration and location

The study was a hospital-based, cross-sectional, descriptive study. The study was done from July 2021 to June 2022. The study was performed at the Jawaharlal Nehru Medical College and Hospital, Aligarh, India. All patients were provided with written consent in their patient authorization form prior to participating in the study.

A total of 100 patients with chronic spontaneous urticaria visiting the hospital were included in the study. Chronic spontaneous urticaria was diagnosed by careful patient history and relevant investigations and provocation tests, wherever applicable, to exclude inducible causes of urticaria including infections.

Inclusion criteria

All patients with chronic spontaneous urticaria, Aged 18 years and above, Males and females and available for follow up were included.

Exclusion criteria

Patients with history of bleeding diathesis, Family history of coagulation disorders, Patients on immunomodulatory agents in the past 15 days, Patients on anticoagulant drugs in the last one week and lost in follow up were excluded.

Written informed consent was obtained from the subjects before enrolment. For every patient a detailed history was taken, including the age at onset, duration of present illness, atopy and thyroid abnormalities, and this was recorded in a proforma. Disease activity was assessed using Urticaria activity score over 7 days (UAS7).[21] UAS7 was graded as urticaria-free=0; well-controlled urticaria=1-6; mild=7-15; moderate=16-27; and severe urticaria=28-42. Baseline D-Dimer, prothrombin time (PT), activated partial thromboplastin time (APTT) was performed. Plasma D-dimer level >250 ng/ml was indicated as raised (manufacturer's instruction). The reference ranges of PT and APTT were 9.5-13.5 seconds and 24-35 seconds, respectively.

Statistical analysis

All the data was compiled and analysed using Statistical Package for Social Sciences (SPSS) version 22. Percentages, mean, and standard deviation were calculated. Statistical correlation was done using Spearman correlation coefficient.

RESULTS

Of the total hundred chronic spontaneous urticaria patients included in the study, majority of the patients belonged to the age group of 20-30 years with a mean age of 28.4± 10.2 years. There were 55 (55%) males and 45 (45%) females

in the study group. The mean duration of urticaria was 25±9.4 months.

Table 1: Basic epidemiologic parameters of the patients

Parameters		N	%
Age (years)	18-20	16	16
	21-30	46	46
	31-40	20	20
	41-50	18	18
Mean age: 28.4±10.2 years			
Sex	Male	55	55
	Female	45	45
Duration (weeks)	6-12	40	40
	12-24	25	25
	24-48	29	29
	>48	6	6
Mean Duration: 25±9.4			

Table 2: Urticaria severity in patients.

Severity	UAS-7 Score	N	%
Mild	7-15	9	9
Moderate	16-27	23	23
Severe	28-42	68	68

Mean UAS-7: 22.6±9.9, UAS-7: Daily Urticaria Activity Severity score in last 7 days

Table 3: Elevation of coagulation markers in urticaria patients

Parameters	Value	N	%
d-dimer (ng/ml)	<250	28	28
	>250	72	72
PT (seconds)	<13.5	45	45
	>13.5	55	55
APTT (seconds)	<35	39	39
	>35	61	61

PT: Prothrombin time; APTT: Activated partial thromboplastin time

The basic epidemiologic parameters of the patients in the study have been summarised in (Table 1). The average UAS-7 value in the patients was 22.63. The baseline UAS-7 was graded as mild, moderate, and severe in 9, 23, and 68 patients respectively (Table 2). Coagulation parameters assessed in our study were elevated in majority of the patients (Table 3). Correlation Between Coagulation Cascade Markers And UAS-7 has been mentioned in (Table 4). D-dimer was raised in 72 (72%) patients. Correlation between D-dimer and UAS-7 days showed that there was a significant covariance between D-dimer and UAS-7 ($p<0.001$, $r=0.93$) (Figure 1). Prothrombin time (PT) was raised in 55 (55%) patients. Significant correlation was found between PT and UAS-7 (p value<0.001, r=0.76) (Figure 2). Raised APTT was observed in 61 (61%) patients. Correlation between APTT and UAS-7 showed that there was a significant covariance between APTT and UAS-7 (p value<0.001, r=0.59) (Figure 3).

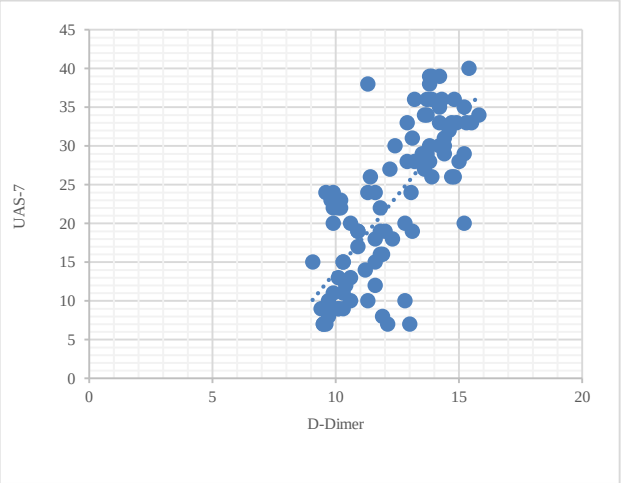

Figure 1: Correlation between d-dimer levels and urticaria activity score-7.

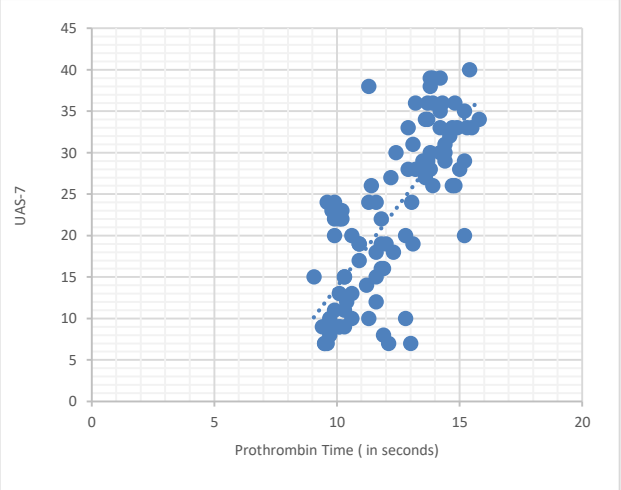

Figure 2: Correlation between prothrombin time and urticaria activity score-7.

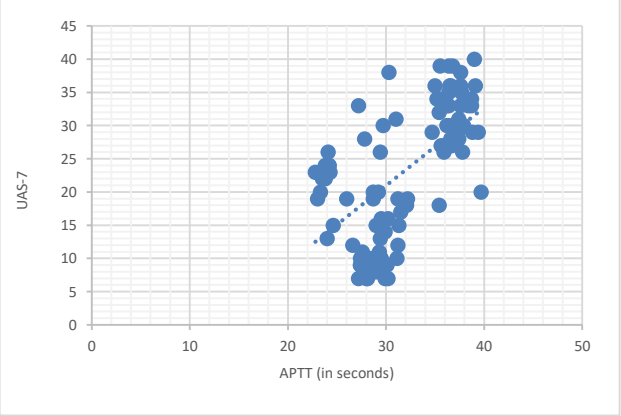

Figure 3: Correlation between activated partial thromboplastin time and urticaria activity score-7.

Table 4: Correlation between coagulation cascade markers and UAS-7.

Parameters	Raised	Mean±SD	P value	Correlation Coefficient ®
d-Dimer	72 /100 (72%)	485.4±406.2	<0.001	0.93
PT	55/100 (55%)	12.3±1.9	<0.001	0.76
APTT	61/100 (61%)	31.4±5.1	<0.001	0.59

DISCUSSION

During the past 3 decades, the incidence of colorectal The pathogenesis of chronic urticaria has for long remained a mystery. The autologous serum skin test shows that histamine releasing factors are present in serum which produces a wheal and flare reaction.

These factors were identified as autoantibodies to IgE and FcεRI receptors in large number of patients, signifying the role of autoimmunity in CSU. These IgG autoantibodies has been detected in large proportion of patients (about 65%) with chronic urticaria and might be involved in the activation of mast cells and basophils with subsequent release of major basic protein and other mediators causing their degranulation.[22] Binding of antibodies to the receptors may activate the complement system and release anaphylotoxins. Histamine release from mast cells has been demonstrated due to the anaphylatoxin 5a and complement system.[22]

The coagulation cascade is involved in the pathogenesis of chronic urticaria patients.[14-17] This was hypothesized based on the observation that autologous plasma skin test may be positive in some patients with a negative autologous serum skin testing.[18-23] The serum levels of prothrombin fragment F1+2 was also found to be high in patients of CSU.[14] Later it was found that the activation of the *in vivo* coagulation process occurs through the extrinsic pathway and is initiated by the binding of factor VII to tissue factor.[24] Activated eosinophils present in the inflammatory infiltrate express tissue factor and parallels disease activity.[15,16] This leads to the generation of thrombin and fibrin degradation products. Thrombin then activates the mast cells, triggering their degranulation, and thereby causes urticaria.[17] Inflammation and coagulation sustain each other to create a loop where the pro-inflammatory cytokines (Interleukin- 1, 6 and tumour necrosis factor – alpha) induce tissue factor, the chief initiator of coagulation pathway, while the coagulation proteins such as factor VIIa, X and IIa induce pro-inflammatory cytokines by acting on the protease activated receptors.[25] Prothrombin time is a marker of extrinsic and common pathway of coagulation.[18] In our study, PT was elevated in 55 (55%) out of the 100 patients. In this study, UAS-7 was found to be higher in patients with raised PT, thereby correlating with the disease severity in chronic urticaria patients. Chauhan et al in their study found PT to be prolonged in 63 out of 100 patients of CSU compared to 58 subjects out of 100 controls.[26]

D-dimer is a sensitive marker of fibrin degradation. It is formed through *in vivo* activation of the coagulation process. It also provides indirect evidence of thrombin generation, which activates mast cell degranulation, and induces vascular permeability.[27,28] Previous studies demonstrated a rise in D-dimer levels in 2/21 (10%), 14/68 (20%) and 58/120 (48.3%) patients, respectively. In our study, D-dimer levels were elevated in 72/100 (72%) CSU patients.[14,15,29] In this study, high UAS-7 was found to be higher in patients with raised D-dimer level. Asero et al. found that d-dimer levels were significantly increased in eight patients with severe chronic urticaria (defined as more than 10 large wheals over body) compared to thirteen patients with slight to moderate urticaria (slight defined as 1-10 wheals of less than 3 cm diameter; moderate defined as 10-50 small wheals or 1-10 large wheals) and normal controls.[17] Triwongwaranat et al in a retrospective study from Thailand found that approximately half patients had elevated d-dimer levels and d-dimer levels were higher in patients with more severe urticaria (measured by daily UAS).[29] Patients with negative autologous plasma skin test were found to have lower levels of d-dimer compared to those with positive test in a case control study from Italy.[30] Patients with high d-dimer levels have been found to respond favourably to heparin and tranexamic acid in some studies.[31] A study from Egypt by Farres et al. found that d-dimer levels significantly correlated with disease activity and fell drastically after disease remission was achieved.[32]

Activation of intrinsic coagulation cascade is initiated by activation of contact factor. The contact system consists of factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen. Activation of the contact system can initiate the coagulation cascade through factor XII activation.[33,34] To date, little is known regarding contact factor activation in CSU. It is plausible that the contact factor activation observed in patients with CSU in the current study was due to the selective deficiency of intrinsic coagulation factors. In this study, APTT were also elevated in 61/100 (61%) chronic urticaria patients signifying an involvement of intrinsic coagulation factors. Kim et al found that APTT showed significant prolongation in patients with CSU compared to controls. It was prolonged in 59.4% patients compared to 5% controls. They also found elevation of d-dimer levels in urticaria but found that PT of patients and controls was statistically similar. Factors involved in the intrinsic coagulation pathway (factors VII, IX and XII) and common pathway (factors II, V, X) were found to be decreased. They also concluded that conventional coagulation tests may not be very sensitive for detection of abnormalities in the coagulation cascade and found that global coagulation

assays such as thrombin generation assays may be more sensitive.[18]

Limitations

It was a non-blinded cross-sectional study and there was no control group for comparison. Further, other markers of the coagulation cascade were not evaluated in our study due to economic reasons. We could not trace the coagulation markers with the disease course. A correlation of the coagulation markers with the markers of inflammation such as C-reactive protein is also desirable, but was not done in our study.

CONCLUSION

In current study, a significant correlation between markers of coagulation cascade like D-Dimer, PT, APTT levels and the disease activity in patients of chronic spontaneous urticaria was seen. These results might directly support the possible involvement of both intrinsic and extrinsic pathways of coagulation in the pathogenesis of chronic spontaneous urticaria. Our study suggests that these markers can help predict the disease severity and possibly monitor therapeutic response. Though global coagulation assays may be more sensitive indicators of urticaria activity, performing these assays may not be feasible in resource poor settings due to economic, and logistical issues. Few studies correlating coagulation assays with the disease severity in urticaria have been performed, which we have attempted. However, the exact role of markers of coagulation cascade in predicting the disease activity needs to be elucidated in further studies with a control group and long-term post treatment follow up.

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