Original Article

Clinicoepidemiologic Features of Chronic Spontaneous Urticaria in Patients with Elevated Plasma D-Dimer Levels versus those without It: A Case–Control Cross-Sectional Study of 100 Indian Patients

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Abstract

Background: Activated coagulation cascade is implicated in urticaria pathogenesis marked by high plasma D-dimer, a marker of fibrinolysis, levels correlating with high urticaria activity score (UAS) and poor therapeutic outcome. **Methods:** Quantitative plasma D-dimer levels and coagulation parameters in 100 (male:female ratio 1:3) Indian patients with chronic spontaneous urticaria and age- and gender-matched healthy controls were compared. The clinicoepidemiologic features of chronic urticaria were then compared among patients with normal (≤0.2 mg/L) and elevated (≥0.3 mg/L) plasma D-dimer levels. **Results:** Plasma D-dimer in 23% patients and 4% controls and prothrombin time and activated partial thromboplastin time in 63% and 5% patients, respectively, were significantly higher compared with 58% and 1% of controls, respectively. About 18 of 72 (25%) patients with high UAS of ≥16–42 were compared with 5 of 28 (17.8%) patients with UAS7 of ≤15. Patients with elevated plasma D-dimer levels had significantly more systemic symptoms (86.9% vs. 81.8%) compared with patients with normal plasma D-dimer levels. **Conclusion:** A subset of patients with chronic urticaria have elevated plasma D-dimer levels and exhibit higher UAS7 and systemic symptoms that may influence long-term prognosis and therapeutic choices. Small number of patients, a cross-sectional nature of study, lack of treatment outcome measures, information on self-medication, and unavailability of specific parameters for coagulation pathway activation remain few limitations of this study.

Keywords: *Activated partial thromboplastin time, angioedema, coagulation cascade, D-dimer, extrinsic coagulation pathway, prothrombin time, urticaria, urticaria activity score*

Introduction

While urticaria affects 15%–20% of population at least once or more during a lifetime, the prevalence of chronic spontaneous urticaria characterized by continuous or recurrent urticarial wheals with or without angioedema for 6 weeks or more is estimated at 0.5%–1% in adults significantly affecting the quality of life.[1,2] Women are affected more often than men, and most patients are between 20 and 40 (mean 33 years) years of age.[3,4] Recurrences are common for months or years in about 30% of patients.[4] Focal bacterial, viral and parasitic infections, foods, drugs, inhalants, systemic diseases, and stress are frequently implicated triggers.[5,6] However, its exact etiology remains obscure in several patients despite extensive investigations. The presence of IgG autoantibodies against epitopes expressed on the α-chain of high-affinity receptor of IgE (FcεRI) in 30%–40% or less commonly against IgE itself (in 5%–10% of patients) raises a possibility of activation of mast cells by allergens that bind to high-affinity receptor FcεRI of specific IgE antibodies in a subset of patients with positive autologous serum skin test diagnosed with autoimmune urticaria.[7-9] Autoallergic mast cell activation too has been suggested as another possible pathomechanism of chronic spontaneous urticaria in patients expressing IgE antibodies against thyroid peroxidase.[10] However, a positive wheal and flare reaction even with IgG-depleted serum indicates possibility of mechanisms other than autoimmunity playing a role in chronic urticaria pathogenesis.[11] Recently, higher positivity of autologous plasma skin testing in 80% of patients

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corresponding to the severity of disease compared with positive autologous serum skin testing (ASST) in 50% of patients suggests activation of coagulation pathway in the pathogenesis of chronic urticaria.[12,13] Low-affinity IgE receptor (FcεRII) autoantibodies have been shown to activate eosinophils to cause mast cell degranulation through release of major basic protein.[14] Eosinophils express tissue factor and activate the extrinsic coagulation pathway resulting in conversion of prothrombin to thrombin by activated factor X generating PF_{1+2} during the process.[15,16] The thrombin thus generated causes urticaria by increasing vascular permeability and plasma extravasation followed by degranulation of skin mast cells.[17-19] Thrombin also acts on fibrinogen to convert it into fibrin that is finally degraded by plasmin to produce fibrin degradation products and plasma D-dimer which can be a possible biomarker for disease severity both for acute and chronic urticaria. This appears plausible given that patients responding to omalizumab therapy too have shown a decrease in elevated plasma D-dimer levels parallel to clinical response when compared with that in nonresponders.[20-22] Furthermore, these patients also showed better therapeutic response to heparin, tranexamic acid, or cyclosporine than antihistamines alone.[20,23,24] We evaluated plasma D-dimer levels in Indian patients with chronic urticaria and their clinicoepidemiologic features. The knowledge will be useful for patients and clinicians alike for choice of treatment modalities in terms of need to recommend antihistamines in higher than recommended doses, addition of immunomodulator drugs, heparin, tranexamic acid, or use of omalizumab just on the basis of signs and symptoms alone for improved therapeutic outcome and long-term prognosis in patients with raised D-dimer levels.

Materials and Methods

One hundred patients (male: female ratio of 1:3) aged 18–69 (mean ± SD 36.12 ± 10.9) years with chronic spontaneous urticaria not responding to recommended doses of antihistamines, and equal number of age- and gender-matched healthy adult controls not on any medication were studied between April 2016 and March 2017. An episode of urticaria was defined as several days of urticarial signs and symptoms with intervening asymptomatic and urticaria-free days. Disease activity and severity grading were calculated on the basis of urticaria activity score (UAS) 7 [Table 1].[1,25] Patients with inducible urticaria, urticarial vasculitis, acute urticaria, systemic diseases (abnormal thyroid function, hepatorenal, hematological, infective or autoimmune disorders), or on medications (aspirin, clopidogrel, warfarin, heparin, antihistamines, corticosteroids, omalizumab) that could influence the course of urticaria or coagulation/fibrinolysis pathway, and pregnant/lactating women were excluded from the study after detailed clinical history/examination, provocation tests, and relevant investigations such as complete blood counts, thyroid and hepatorenal function tests, antithyroid peroxidase antibodies, fasting blood glucose estimation, HBsAg, and antistreptolysin O titer, tests for antinuclear antibody and rheumatoid factor, urinalysis, and stool microscopy for ova/cysts. Other laboratory tests in all patients with urticaria included C-reactive protein (CRP) and absolute eosinophil count (AEC), the possible biomarkers of inflammation and coagulation pathway and urticaria activity.[16,26]

Plasma D-dimer levels were estimated quantitatively in all patients and controls by immunometric flow through method using NycoCard test kits (Nycomed Pharma, Oslo, Norway) as per manufacturer's instructions. Plasma D-dimer levels ≥0.3 mg/L were considered elevated (normal levels ≤0.2 mg/L as per manufacturer's manual). Coagulation parameters such as thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT) were assayed in all study subjects by the use of calcium thromboplastin to measure the clotting time of the patient's plasma using STA Compact® and STA-R® Neoplastine kit marketed by

Table 1: UAS7[1] and severity grading[25]

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild but not annoying
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

UAS7 is sum of UAS of 0-6 for each day over 7 consecutive days (maximum score 42)

Severity grading

0, Itch and hive-free and indicative of no symptoms of CSU

16, Well-controlled urticaria

7-15, Mild urticaria

16-27, Moderate activity urticarial

28-42, Severe activity urticaria

UAS=Urticaria activity score; CSU=Chronic spontaneous urticaria

Diagnostica Stago (Asnieres, France) and comparing it with that of a normal standard.

The patients were divided into two groups, Group A and Group B, for comparison of clinicoepidemiological features on the basis of patients with elevated and normal plasma D-dimer levels, respectively.

Statistical analysis

Median ± interquartile range (IQR) was calculated in case of extreme values with wide and uneven distribution (outliers and non-normal data). Mann–Whitney *U* test was used to compare nonparametric and unevenly distributed data. Chi-square test and Student's *t*-test were used for statistical analysis of the categorical and parametric data, respectively. A *P* value < 0.05 calculated at 5% level (95% confidence limit) was considered statistically significant.

Results

The baseline clinicodemographic and investigative data for D-dimer and coagulation profile of all patients and controls are shown in Table 2. The majority of [68 (68%)] patients were between 18 and 40 years of age with higher prevalence in women. The duration of urticaria was 6 weeks to 240 (median ± IQR = 6± 9) months and

Table 2: Baseline characteristics of patients and controls

Baseline characteristics		No. of patients (%) *n*=100	No. of controls (%) *n*=100	*P*
Gender	Males (M)	25	25	
	Females (F)	75	75	
	M: F	1:3	1:3	
Age (in years)	Range	18-69	19-70	
	Mean±SD	36.1±10.9	38.3±12.2	0.18
	18-30	37	30	
	>30-40	31	29	
	>40-50	23	29	
	>51	9	12	
Duration of urticaria (in months)	Range	1.5-240	-	
	Median±IQR	6±9	-	
	1.5-12	85	-	
	>12-25	7	-	
	>25-37	3	-	
	>37-48	1	-	
	≥48	4	-	
Age at onset of urticaria (in years)	Range	3-69	-	
	Mean±SD	33.53±11.4	-	
	≤10	2	-	
	>10-20	7	-	
	>20-30	36	-	
	>30-40	29	-	
	>40-50	19	-	
	>50-60	6	-	
	>60	1	-	
D-dimer levels (normal ≤0.2 mg/L)	≥0.3	23	4	0.0001*
PT (normal=11.4-13.7 s)	>13.7	63	58	
	≤13.7	37	42	
	Range	10.9-26.7	10.3-20.5	0.039*
	Mean±SD	15.00±2.92	14.27±1.93	
aPTT (normal=27.8-41.8 s)	>41.8	5	1	
	≤41.8	95	99	
	Range	19.2-42.5	19.3-42.0	0.039*
	Mean±SD	33.15±5.25	31.66±4.90	
TT (normal=15-18 s)	>18	8	6	
	≤18	92	94	
	Range	15.1-19.1	13.5-20.3	<0.0001*
	Mean±SD	17.04±0.72	16.92±0.86	

SD=Standard deviation; IQR=Interquartile range; PT=Prothrombin time; aPTT=Activated partial thromboplastin time; TT=Thrombin time, Mann-Whitney *U* test was used to compare nonparametric and unevenly distributed data. Chi-square test and Student's *t*-test were used for statistical analysis of the categorical and parametric data, respectively; **P*<0.05 was considered statistically significant

the majority [85 (85%)] of patients had urticaria for less than 12 months. The age at onset of urticaria ranged from 3 to 69 (mean ± SD = 33.5 ± 11.4) years and 84 (84%) patients started having urticaria at 21–50 years. Only 23 (23%) patients and 4 (4%) controls had elevated plasma D-dimer levels of ≥0.3 mg/L and the difference was statistically significant ($P < 0.0001$). The mean values for PT (15.00 ± 2.92 vs. 14.27 ± 1.93), aPTT (33.15 ± 5.25 vs. 31.66 ± 4.90), and TT (17.04 ± 0.72 vs. 16.92 ± 0.86) were significantly higher in patients than controls ($P < 0.05$).

Table 3 depicts comparative clinicoepidemiologic features of patients with elevated plasma D-dimer (Group A) and normal values (Group B) with no statistically significant difference in age, gender, age at onset, duration, and mean number (52.8 ± 46.9 vs. 70 ± 37.2 episodes per year) of recurrences of urticaria and/or angioedema. Eighteen of 23 (78.3%) patients with higher UAS7 of ≥16–42 had significantly elevated plasma D-dimer levels compared with 5 of 23 (21.7%) patients with UAS7 of ≤15 ($P = 0.0001$).

Except for a statistically significant higher percentage, 19 of 23 (82.6%) patients in Group A showing increased PT compared with 44 of 77 (57.1%) patients in Group B; the coagulation parameters did not differ significantly in both the groups [Table 4]. There was no statistically significant difference in CRP or AECs in patients in both the groups.

Clinically, one or more additional systemic symptoms were present in 20 (86.9%) and 63 (81.8%) patients in Group A and Group B, respectively [Table 5]. General

Table 3: Comparison of characteristics of urticaria patients in Group A and Group B

Characteristics of patients		Group A (D-dimer levels ≥0.3 mg/L) No. of patients (%) *n*=23	Group B (D-dimer levels ≤0.2 mg/L) No. of patients (%) *n*=77	*P**
Gender	Males (%)	5 (21.7)	20 (25.9)	
	Females (%)	18 (78.3)	57 (74.1)	
	Male: female	1:3.6	1:2.9	
Age in years	Range	24-55	18-69	
	Mean age±SD	38.08±10.53	39.62±10.81	0.55
Age at onset (in years)	Range	20-55	3-68	
	Mean±SD	36.52±9.42	32.64±11.8	0.15
	≤20	1 (4.3)	8 (10.4)	
	>20-30	7 (30.4)	29 (37.7)	
	>30-40	5 (21.7)	24 (31.2)	
	>40-50	9 (39.3)	10 (12.9)	
	>50-60	1 (4.3)	5 (6.5)	
	>60	0	1 (1.3)	
Duration of urticaria (in months)	Range	2-48	1.5-240	
	Median±IQR	5±4	6±9	0.61
	≤12	21 (91.4)	64 (83.1)	
	>12-25	1 (4.3)	6 (7.8)	
	>25-37	0	3 (3.9)	
	>37-48	1 (4.3)	0	
	≥48	0	4 (5.2)	
No. of previous episodes of urticaria	10-39	3 (13.0)	7 (9.1)	
	40-69	0	6 (7.8)	
	70-99	0	4 (5.1)	
	100-130	2 (40)	9 (11.7)	
	Mean±SD	52.8±46.9	70±37.2	0.07
No. of episodes of urticaria with angioedema	0	17 (73.9)	46 (59.7)	
	1-10	6 (26.1)	26 (33.8)	
	11-20	0	1 (1.3)	
	21-30	0	2 (2.6)	
	>30	0	2 (2.6)	
	Mean±SD	1.3±0.81	1.74±1.21	0.10
UAS7 and severity grading	Up to 15 (mild)	5 (21.7%)	23 (29.9)	0.44
	≥16-42/(moderate to severe)	18 (78.3%)	54 (70.1)	0.44
	Mean±SD	5.48±1.50	5.25±1.33	0.48

SD=Standard deviation; IQR=Interquartile range; UAS=Urticaria activity score, MannWhitney *U*-test was used to compare nonparametric and unevenly distributed data. Chi-square test and Student's *t*-test were used for statistical analysis of the categorical and parametric data, respectively; **P*<0.05 was considered significant

Table 4: Coagulation profile and other laboratory parameters in Group A and Group B patients

Laboratory parameters		Group A (D-dimer levels ≥0.3 mg/L) No. of patients (%) *n*=23	Group B (D-dimer levels ≤0.2 mg/L) No. of patients (%) *n*=77	*P*
PT (normal=11.413.7 s)	>13.7	19 (82.6)	44 (57.1)	0.03*
	≤13.7	4 (17.4)	33 (42.9)	
	Range	11.4-21.9	10.9-26.7	
	Mean±SD	15.29±2.71	14.91±2.99	0.57
aPTT (normal=27.841.8 s)	>41.8	2 (8.7)	3 (3.9)	0.79
	≤41.8	21 (91.3)	74 (96.1)	
	Range	21.1-42.5	19.2-42.1	
	Mean±SD	33.69±5.28	32.984±5.26	0.57
TT (normal=15-18 s)	>18	1 (4.5)	7 (9.1)	0.27
	≤18	22 (95.5)	70 (90.9)	
	Range	15.8-18.4	15.1-19.1	
	Mean±SD	17.10±0.54	17.01±0.76	0.60
AEC (normal=20-500 cells/mm^3)	Range	70-540	20-870	0.94
	Mean±SD	204.70±132.8	207.18±152.6	
Positive CRP	Positive	2 (8.7%)	1 (1.3%)	0.70
	Negative	21 (91.3)	76 (98.70	

PT=Prothrombin time; SD=Standard deviation; aPTT=Activated partial thromboplastin time; TT=Thrombin time; AEC=Absolute eosinophil count; CRP=C-reactive protein, Mann-Whitney *U* test was used to compare nonparametric and unevenly distributed data. Chi-square test and Student's *t*-test were used for statistical analysis of the categorical and parametric data, respectively; *P<0.05 was considered significant

Table 5: Comparison of systemic symptoms in Group A and Group B patients

Individual associated systemic symptoms	Group A No. of patents (%) *n*=23	Group B No. of patents (%) *n*=77	*P**
No. of symptomatic patients	20 (86.9)	63 (81.8)	0.0003*
No. of symptoms			
1-3	18 (78.3)	58 (75.3)	-
4-5	2 (8.7)	5 (6.5)	-
General symptoms (headache, malaise, lassitude, loss of concentration, feverish feel)	15 (65.2)	8 (10.4)	0.32
Feeling of hot or cold	8 (34.7)	24 (31.1)	0.09
Flushing	7 (30.4)	13 (16.8)	0.43
Joint symptoms (pain, swelling)	5 (21.7)	13 (16.8)	0.28
Gastrointestinal symptoms (nausea, vomiting, diarrhea, indigestion, pain abdomen)	5 (21.7)	13 (16.8)	0.28
Cardiorespiratory symptoms (syncope, palpitations, breathlessness/wheeze)	2 (8.6)	9 (11.6)	0.26

Most patients had multiple symptoms. Mann-Whitney *U* test was used to compare nonparametric and unevenly distributed data. Chi-square test and Student's *t*-test were used for statistical analysis of the categorical and parametric data, respectively; *P<0.05 was considered significant

symptoms (malaise, loss of concentration, lassitude, headache, feverish feel) in 15 (65.2%), gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) in 5 (21.7%), joint symptoms (pain, swelling) in 5 (21.7%), feeling of hot and cold in 8 (34.7%) and flushing in 7 (30.4%) affected more patients in Group A compared with those in Group B. On the other hand, a higher percentage (11.6%) of patients in Group B experienced cardiorespiratory symptoms (syncope, palpitations, breathlessness/wheezing) compared with 8.6% patients in Group A.

Discussion

The demographic profile of the studied 100 patients is similar to what is described in dermatology literature.[3-7] An etiopathogenetic link between chronic urticaria and activation of extrinsic followed by intrinsic coagulation cascades has been suggested by many researchers.[12,15,27-29] The significantly higher mean levels of PT, aPTT, and TT in patients indicates activation of extrinsic with intrinsic coagulation cascade in patients with chronic urticaria. Similarly, activation of coagulation pathway has been reported by other researchers marked by significantly higher levels of D-dimer, a marker of fibrinolysis, and plasma PF_{1+2}, marker of thrombin generation, in patients with chronic urticaria corresponding to disease severity and UAS.[12,15,26,30] Increased levels of plasma D-dimer and factor VIIa in patients with active urticaria correlating with disease severity and fall in their levels observed after urticaria remission further reflects activation of coagulation

pathway in urticaria.[27,28] The higher plasma D-dimer levels in our 23% of patients compared with 4% of controls with a statistically significant difference ($P < 0.05$) also gives credence to these observations.

Urticaria is reportedly more severe in patients with higher plasma D-dimer levels and is seen to correspond with severe urticaria compared with mild disease. A positive correlation between disease severity and elevated plasma D-dimer levels in 48.3% of patients was observed as the levels decreased with reduced urticaria severity in three patients under follow-up in a study.[31] Urticaria also appears resistant to antihistamines in patients with high plasma D-dimer levels and said to improve or show better therapeutic response to treatment with heparin or tranexamic acid, a plasminogen activation inhibitor.[20] The significantly higher UAS7 of ≥16–46 in 18 of 72 (25%) patients with elevated plasma D-dimer levels and in greater percentage of patients, 78.3% in Group A, also reflects an association between disease severity and elevated plasma D-dimer levels. Similar observations have been made previously as well.[15,30-32] Asero *et al.*[15] observed moderate to severe disease activity in 75% and 38% of patients showing elevated and normal plasma D-dimer levels, respectively. Takahagi *et al.*[32] also observed above normal levels of plasma D-dimer in 35% of patients with chronic urticaria and its severity correlating with fibrin degradation products and plasma D-dimer levels. The systemic symptoms in our 86.9% of Group A patients were significantly higher compared with 81.8% of patients in Group B. Although the difference was not statistically significant, general symptoms of being unwell, gastrointestinal symptoms, feeling of hot and cold, flushing, and joint pains were more frequent in Group A patients, whereas cardiorespiratory symptoms were comparatively more frequent in Group B patients.

Limitations

Small number of patients, a cross-sectional nature of study, unavailability of specific parameters to determine coagulation pathway activation, and lack of information on self-medication are some of the limitations of this study. Treatment outcome measures were not part of the study.

Conclusion

It appears that a subset of patients with chronic spontaneous urticaria have coagulation cascade activation marked by elevated plasma D-dimer levels and exhibit a higher UAS and systemic symptoms. On the contrary, blood levels of eosinophils may not be elevated as was also observed in both the groups in this study, and positive CRP was found only in a minority of our patients as was also seen in a previous study suggesting a reduced sensitivity of these parameters.[16,26] In light of our observations, we tend to agree with Farres *et al.*[27] that plasma D-dimer and PF_{1+2} may be useful for monitoring disease activity despite a weak correlation between UAS and plasma D-dimer levels. However, the exact role of D-dimer in predicting disease activity needs to be elucidated further after large systematic studies and long-term post treatment follow-up given that our 77% of patients also had normal levels.

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Conflicts of interest

There are no conflicts of interest.

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