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Severe CSU and Activation of the Coagulation/ Fibrinolysis System: Clinical Aspects

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Key words
chronic urticaria; D-dimer; coagulation biomarkers; inflammation

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Doi
10.23822/EurAnnACI.1764-1489.109

Summary
Background. *About 50% of patients with severe chronic spontaneous urticaria (CSU) show signs of activation of the coagulation/fibrinolysis system, but the clinical significance of this phenomenon is unclear.* **Objective.** *The present study compared patients with severe CSU showing and not showing elevated D-dimer plasma levels.* **Methods.** *132 adult patients (m/f 44/88; mean age 51, 5 years; range 14 - 89 years) with severe CSU (UAS-7 > 30) were included in a cross-sectional, real life study. The study group was divided based on baseline D-dimer plasma levels, and compared for age, sex, disease duration, disease activity, CRP, thyroid autoimmunity, total IgE, and atopic status.* **Results.** *Identical numbers of patients showed elevated and normal D-dimer plasma levels (50% and 50%, respectively). Patients showing elevated D-dimer levels were slightly older ($p < 0.05$), were more frequently females ($p < 0.05$), had a longer disease duration ($p < 0.01$), and had a significantly higher prevalence of elevated PCR (26/66 vs 4/66; $p < 0.001$).* **Conclusions.** *Only 50% of patients with severe CSU show elevated D-dimer plasma levels. The activation of the coagulation/fibrinolysis system is associated with a systemic inflammatory milieu, suggesting the existence of a specific phenotype. Whether this reflects the existence of different endotypes in patients showing and not showing the activation of the coagulation cascade has still to be established.*

Introduction

The frequent occurrence of intense thrombin generation in patients with chronic spontaneous urticaria (CSU) was first described about 12 years ago (1). Such phenomenon, which is clearly associated with disease severity (2), seems to occur via the activation of the extrinsic pathway of the coagulation cascade (1). This finding was confirmed over time by several research groups (3-6), one of whom also showed that the activation of the extrinsic pathway of the coagulation might in turn activate the intrinsic pathway also, eventually producing a hyper-coagulable pattern (7). The activation of the coagulation / fibrinolysis system is possibly a consequence of the hyper-expression of tissue factor by activated eosinophils (8), although also endothelial cells seem able to play a role in this sense (9). The activation of the coagulation system in CSU occurs irrespectively of the presence or absence of autoreactivity (5,10), and has been shown to be negatively associated with patients' response to second-generation antihistamines (11). Although increased plasma levels of D-dimer are not predictive of CSU patients' response to the humanized anti-IgE mAb, omalizumab (12), it nonetheless parallels the clinical response to this drug (13). Patients with severe CSU show a detectable activation of the coagulation cascade in about 50% of cases (12). What differentiates patients with severe CSU showing and not showing the activation of the coagulation / fibrinolysis system has not been established so far. The present study compared the clinical features in these two subsets of patients with CSU.

Patients and methods

Patients

This cross-sectional, real life study included 132 patients (m/f 44/88; mean age 51, 5 years; range 14-89 years) with severe CSU (UAS-7 > 30) unresponsive to antihistamine treatment. The study group was divided based on baseline D-dimer plasma levels, which were measured by ELISA and expressed as ng/

ml; values exceeding 500 ng/ml were considered elevated. The following parameters were investigated: age, sex, disease duration (in months), disease activity (expressed as UAS-7 value), CRP, thyroid autoimmunity (defined as the presence of circulating IgG autoantibodies specific for thyroperoxidase and/or thyroglobulin), total IgE, and atopic status (defined as a positive history of respiratory and/or food allergy confirmed by positive SPT with commercial allergen extracts). Patients gave an informed written consent to the use of their data in anonymous form. Since the study was retrospective and based on routine diagnostic tests, a formal approval by an external ethical committee was not required.

Statistics

Means and proportions were compared by two-tailed Student's t-test and by chi-square test with Yates' correction, respectively. Probability values less than 5% were considered statistically significant.

Results

Results are summarized in **table I**. D-dimer plasma levels were elevated in 66 (50%) patients and normal in 66 (50%) patients, respectively. The two groups did not differ in terms of UAS-7 score, but patients showing elevated D-dimer levels showed a slight, albeit statistically significant difference in mean age (54.3 years vs 48.7 years; $p < 0.05$), and a higher prevalence of female patients (m/f 16/50 vs 28/38; $p < 0.05$). Further, this subgroup showed a significantly longer disease duration than patients showing normal D-dimer levels (mean 64.6 months [range 2-600 month; median 21 months] vs mean 28.6 months [range 2-500 months; median 6 months] $p < 0.01$). Atopic status (19/66 [29%] vs 15/66 [23%], in patients with elevated or normal D-dimer, respectively; p = ns), elevated total IgE (51% vs 52%, respectively; p = ns), and thyroid autoimmunity (14/66 [21%] vs 19/66 [29%], respectively; p = ns) were similarly distributed in the two groups. In contrast, the activation of the coagulation / fibrinolysis system was associated with a significantly higher prevalence of elevated PCR (26/66 vs 4/66; $p < 0.001$).

Discussion

Although the coagulation / fibrinolysis cascade can be activated in patients with CSU, and this event is unquestionably associated with a severe disease (2), not all patients with severe CSU do show elevated D-dimer plasma levels. This study, which was focused specifically on subjects with severe CSU (UAS-7 > 30) refractory to antihistamine treatment, confirmed that elevated D-dimer plasma levels are found only in 50%. The reasons for this are not yet clear. Patients showing signs of activation of the coagulation / fibrinolysis system were frequently older females with a longer disease duration showing a systemic inflammatory milieu, as suggested by the higher frequency of elevated CRP, a non-specific marker of inflammation. In a recent study, about one third of CSU patients showed elevated CRP levels, often in association with a positive autologous serum skin test, a marker of autoreactivity (14). The association between coagulation / fibrinolysis and inflammation markers has been observed about 9 years ago (15) and confirmed more recently (16,17). Altogether, these findings seem to suggest the existence of a phenotype of CSU characterized by more intense, clinically detectable inflammatory events, as also shown by studies that investigated different inflammation markers (18,19), that would involve the coagulation system. On the other hand, this study suggests that severe CSU may occur in the absence of any clinically detectable inflammation. Whether this reflects the existence of different endotypes in patients showing and not showing the activation of the coagulation cascade has still to be established.

***Table I** - Clinical features of patients with severe CSU with or without signs of fibrinolysis.*

	elevated D-dimer	**normal D-dimer**	**p**
no.	66	66	
mean age (years)	54.3	48.7	< 0.05
females	50 (76%)	38 (56%)	< 0.05
disease duration (months) [median]	64.6 [21]	28.6 [6]	< 0.01
elevated CRP	26 (39%)	4 (6%)	< 0.001
atopic status	19 (29%)	15 (23%)	ns
thyroid autoimmunity	19 (29%)	14 (21%)	ns
elevated total IgE	19/37 (51%)	22/42 (52%)	ns

ns, not significant.

The inflammatory milieu involving the activation of coagulation / fibrinolysis system does not seem to interfere with the clinical response to omalizumab (12), suggesting that the activated coagulation cascade probably acts as a secondary amplification mechanism rather than the leading actor in this disease. The inflammatory milieu suddenly normalizes in CSU patients responding to omalizumab (13), suggesting that the interaction between autoreactive IgE (20) and their ligands is a likely starting point of the inflammation process, and that their neutralization by anti-IgE leads to the "shutdown" of the whole mechanism. Patients showing elevated D-dimer levels are often unresponsive to antihistamines (11,16), but this seems the case also in patients lacking signs of systemic inflammation, as shown by the present study.

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