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D-dimer Plasma Concentration in Chronic Urticaria Patients with Positive Autologous Serum Intradermal Test

Stężenie D-dimerów w osoczu chorych na przewlekłą pokrzywkę wykazujących dodatni wynik testu śródskórnego z surowicą autologiczną

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Abstract

Background. Increased blood concentration of D-dimer has been observed in patients with various autoimmune disorders, indicating activation of the coagulation and fibrinolytic cascades.
Objective. Assessment of D-dimer concentration in the peripheral blood of patients suffering from chronic urticaria with positive response to the autologous serum skin test (ASST), which suggests autoimmunological cause of the disease and is a useful screening test for autoimmune urticaria.
Material and Methods. Plasma concentration of D-dimer, an index of active fibrinolysis, was measured in 26 patients with positive ASST (6 men and 20 women) suffering from chronic urticaria and 30 healthy subjects (7 men and 23 women) using enzyme-linked immunosorbent assay (ELISA) kits.
Results. There were no significant differences in D-dimer plasma concentrations between the two groups.
Conclusions. It seems that in the course of chronic urticaria with positive ASST, enhanced fibrinolytic activity does not occur in the peripheral blood, as expressed by plasma D-dimer concentration (**Adv Clin Exp Med 2007, 16, 1, 65–68**).

Key words: urticaria, fibrinolysis, D-dimer, autologous serum skin test.

Streszczenie

Wprowadzenie. Zwiększone stężenie D-dimerów we krwi obserwowano u chorych na różne choroby autoimmunologiczne, co wskazuje na aktywację kaskady krzepnięcia i fibrynolizy.
Cel pracy. Ocena stężenia D-dimerów we krwi obwodowej chorych na przewlekłą pokrzywkę, u których stwierdzono dodatni wynik testu skórnego z surowicą autologiczną (ASST), który sugeruje autoimmunologiczną przyczynę tej choroby i jest użytecznym testem przesiewowym w diagnostyce pokrzywki autoimmunologicznej.
Materiał i metody. W osoczu 26 chorych na przewlekłą pokrzywkę (6 mężczyzn i 20 kobiet), wykazujących dodatni ASST, oraz u 30 zdrowych osób (7 mężczyzn i 23 kobiet) oznaczono stężenie D-dimerów (wskaźnik aktywacji fibrinolizy) z użyciem metody immunoenzymatycznej (ELISA).
Wyniki. Nie obserwowano statystycznie istotnych różnic w stężeniu D-dimerów pomiędzy badanymi grupami.
Wnioski. Można przypuszczać, iż w przebiegu przewlekłej pokrzywki z dodatnim wynikiem ASST nie występuje wzmożona aktywność fibrynolityczna we krwi obwodowej, wyrażona osoczowym stężeniem D-dimerów (**Adv Clin Exp Med 2007, 16, 1, 65–68**).

Słowa kluczowe: pokrzywka, fibrynoliza, D-dimery, test skórny z surowicą autologiczną.

The etiology and pathogenesis of chronic urticaria are poorly understood; however, in 30–50% of cases, autoimmune processes have been suggested as causative factors [1, 2]. It has been reported that mast cells may show profibrinolytic activity [3, 4]. The supernatants of cultured mast cells are capable of inducing the conversion of plasminogen to plasmin and of lysing a fibrin clot

[3, 5]. Moreover, it has been demonstrated that skin mast cells may affect hemostasis by prolonged bleeding time and by inhibiting thrombin formation [6]. Interestingly, a double-blind placebo-controlled study showed a response of chronic idiopathic urticaria to warfarin, but the mechanism of such effect is unclear [7]. Moreover, it has been reported that patients with chronic urticaria show skin reactivity to the autologous serum skin test (ASST) inhibited by heparin [8], whereas heparin may prove useful in the treatment of chronic urticaria [9].

It has been reported that patients suffering from some autoimmune diseases are characterized by increased plasma D-dimer concentration, reflecting a potential activation of both the coagulation and fibrinolytic cascades [10]. Measuring markers of hemostasis is useful in evaluating disease activity and in monitoring therapy in patients with some immune-mediated diseases [10–12].

Considering the above, the question was posed whether there are any alterations in systemic fibrinolytic function in patients suffering from chronic urticaria with positive response to the ASST, suggesting, then, an autoimmunological cause of the disease. Such tests may reveal the presence of functional autoantibodies to FcεRI and/or IgE in urticaria patients and are used in clinical practice to assess the autoimmune origin of a disorder [1, 2]. In this study, the plasma concentrations of D-dimer (an indirect marker of coagulation activation followed by reactive fibrinolysis) of patients with positive ASST suffering from chronic urticaria and healthy subjects were compared.

Material and Methods

The study group consisted of 26 non-smoking patients (20 females and 6 males, median age: 30 years, range: 18–41 years) with chronic urticaria who responded positively to ASST. All other identified causes of urticaria had been excluded by appropriate investigation. Those with physical urticaria were not included in the study. Their disease was characterized by recurrent hives occurring at least four times a week for more than eight weeks. Urticarial activity was measured by applying the scale of 0–3 (sum of score: 0–6) proposed by Zuberbier et al. [13]. Patients scoring 4 or more were included in the study. The control group consisted of 30 healthy subjects who responded negatively to the ASST (23 women and 7 men, median age: 31 years, range: 19–40 years).

Blood Collection and Plasma Preparation

Blood was obtained in the morning (7:00 to 8:00 a.m., in the fasting state at least 12 hours) after 60 minutes of rest, with slight or no stasis, from the antecubital vain directly into plastic tubes containing anticoagulant.

Autologous Serum Skin Test (ASST)

The intradermal tests with patients' own serum were performed according to the method described by Sabroe et al. [1].

D-dimer Assay

The plasma D-dimer level was measured by ELISA following standard procedures (Asserachrom® D-Di kit, Diagnostica Stago, France).

Statistical Analysis

Data are presented as medians with ranges. Comparisons between the two groups were performed by Mann-Whitney's unpaired rank sum test. Correlation coefficients were obtained by the Spearman test. p values below 0.05 were considered significant.

Results

There were no significant differences in plasma concentrations of D-dimer between the patients and the control subjects (Tab. 1). Moreover, no significant association was found between the duration of urticaria and plasma concentration of D-dimer in the patient group ($r = 0.26$, $p = 0.19$).

Discussion

Few studies have investigated the role of fibrinolysis in urticaria, to show contradictory and inconclusive results. Some systemic and local hemostatic abnormalities have been demonstrated in patients with different forms of urticaria [14, 15]. On the other hand, Boonk et al. [16] and Haustein [17] did not find any significant abnormalities in either systemic or local fibrinolysis in lesional skin, suggesting that fibrinolysis does not appear to play an important role, if any, in most cases of chronic urticaria.

D-dimer is a degradation product of cross-linked fibrin by plasmin and is functionally related

Table 1. Plasma concentrations of D-dimer in chronic urticaria patients with positive ASST and in healthy controls

Tabela 1. Stężenie D-dimerów w osoczu chorych na przewlekłą pokrzywkę, u których stwierdzono dodatni ASST oraz osób zdrowych

Analyzed parameter – unit (Badany wskaźnik – jednostka)	Healthy controls (Grupa kontrolna) (n = 30)	Patients (Pacjenci) (n = 26)	Statistical analysis (Analiza statystyczna) *p*
	median range	median range	
D-dimer (ng/ml)	141 20–345	156 25–300	NS

n – number of subjects.

n – liczba badanych.

to the urokinase-type plasminogen activator system. The present authors previously demonstrated that there are no differences between chronic urticaria patients and controls with respect to the urokinase system-associated proteins [18]. Elevated D-dimer concentration reflects increased fibrin formation followed by its degradation [19]. Interestingly, fibrin degradation products may have pharmacological activity [20] and may enhance histamine action as well as other mediators of inflammation [14]. Increased plasma concentration of D-dimer has been demonstrated in different clinical conditions, including immune and inflammatory diseases, reflecting a hypercoagulable state, with or without overt thrombosis. In the present study, no significant differences were found in the plasma concentrations of fibrin D-dimer of patients suffering from chronic urticaria with positive response to the ASST and healthy subjects, suggesting that this subclass of urticaria may not be accompanied by increased plasma fibrin turnover. The results are consistent with those of Boonk et al. [16], who found normal blood concentrations of fibrin degradation products in patients with chronic idiopathic urticaria and physical urticaria, making hyperfibrinolysis unlikely.

Taken together, it seems that in the course of chronic urticaria with positive ASST (useful for autoimmune urticaria screening), enhanced fibrinolytic activity in the peripheral blood does not occur, as expressed by plasma D-dimer concentration. However, to identify precisely the patients with autoimmune urticaria, more tests should be performed to include the surface expression of the activation marker CD63 on basophils using flow cytometry or *in vitro* basophil histamine release assay. Moreover, these findings have confirmed some earlier studies, suggesting that systemic fibrinolysis may not be involved in chronic urticaria.

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