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Plasma Concentration of Platelet Factor 4 in Patients with Acute Urticaria in the Course of Acute Respiratory Tract Infection*

Stężenie czynnika płytkowego 4 w osoczu chorych na ostrą pokrzywkę w przebiegu ostrej infekcji dróg oddechowych

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Abstract

Background. Blood platelets may be activated during hypersensitivity reaction and different inflammatory processes. However, significance of these cells in urticaria has been poorly investigated.
Objectives. To assess platelet secretory activity in patients with acute urticaria, presumably caused by infectious agents.
Material and Methods. Plasma concentration of platelet factor 4 (PF-4) as an indicator of platelet activation was measured in 8 adult patients with acute urticaria and age- and sex-matched 15 healthy controls, using the enzyme-linked immunosorbent assay (ELISA). All patients showed acute symptoms of respiratory tract infection. In addition, C-reactive protein (CRP) concentration in plasma was measured using the immunoturbidimetric assay.
Results. There were no significant differences in plasma concentration of PF-4 between the patients and the control subjects. CRP plasma concentration was significantly higher in the patients than in the controls. We did not find any significant correlation between PF-4 and CRP plasma concentrations in patients with acute urticaria.
Conclusions. It seems that secretory activity of platelets assessed by PF-4 plasma concentration is not enhanced in patients with acute urticaria in the course of acute respiratory tract infection (**Adv Clin Exp Med 2006, 15, 6, 995–998**).

Key words: platelet activation, platelet factor 4, respiratory tract infection, acute urticaria.

Streszczenie

Wprowadzenie. Płytki krwi mogą być aktywowane podczas reakcji nadwrażliwości i różnych procesów zapalnych. Znaczenie tych komórek w pokrzywce jest jednak mało poznane.
Cel pracy. Ocena aktywności sekrecyjnej płytek krwi u chorych na ostrą pokrzywkę przypuszczalnie wywołaną infekcją.
Materiał i metody. Do oceny aktywności płytek krwi zastosowano pomiar stężenia czynnika płytkowego 4 (PF-4) w osoczu za pomocą metody immunoenzymatycznej (ELISA). Badaniem objęto 8 dorosłych chorych na ostrą pokrzywkę oraz 15 zdrowych osób dobranych pod względem wieku i płci. Wszyscy chorzy mieli objawy ostrego zakażenia dróg oddechowych. Oznaczono ponadto stężenie białka C-reaktywnego w osoczu za pomocą metody immunoturbidymetrycznej.
Wyniki. Nie wykazano statystycznie istotnych różnic w osoczowym stężeniu PF-4 u chorych w porównaniu z osobami zdrowymi. Stężenie CRP w osoczu było istotnie większe w grupie osób chorych niż w grupie kontrolnej. Nie stwierdzono istotnej korelacji między stężeniami PF-4 i CRP w osoczu chorych na ostrą pokrzywkę.
Wnioski. Aktywność sekrecyjna płytek krwi, oceniana na podstawie stężenia PF-4 w osoczu, nie zwiększa się u chorych na ostrą pokrzywkę w wyniku ostrego zakażenia dróg oddechowych (**Adv Clin Exp Med 2006, 15, 6, 995–998**).

Słowa kluczowe: aktywacja płytek, czynnik płytkowy 4, infekcje dróg oddechowych, ostra pokrzywka.

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Blood platelets play critical roles in hemostasis and also participate actively in different type response associated with inflammation, hypersensitivity, and infection [1–3]. They share structural and functional similarities with granulocytes and are involved in protection against infection by phagocytosis of pathogens and by secreting chemokines which attract leukocytes [3, 4]. Interestingly, it has been suggested that human platelets possess, and can be stimulated to release, antimicrobial peptides, including platelet factor 4 (PF-4) in response to inflammation mediators [4]. PF-4, an alpha-chemokine containing the CXC, is a sensitive and specific marker of platelet alpha-granule release reaction *in vivo* [5], involved in various immune and inflammatory processes [1, 2, 6].

Acute urticaria (AU), usually considered a hypersensitivity reaction, shows undoubtedly some causal relationship with drugs and infections as viral, bacteria and parasite infections may trigger urticaria symptoms. Infection appears to be the most common cause of AU during childhood [7]. Basing upon a follow-up study of 50 adults, Aoki et al. suggest that acute urticaria is an immunologicaly erroneous reaction to foreign body innoculations, great majority of which are acute infections [8]. Zuberbier et al. emphasised potential importance of upper respiratory tract infections (39.5%) as AU underlying cause [9].

Possible mechanisms involved in infection-associated AU may be those of allergic or nonallergic hypersensitivity, including specific IgE-mediated reactions to bacterial antigens, such as *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenzae* [10]. Moreover, an immediate-type reaction to viral antigens has been demonstrated as mice infected with flu virus developed virus-specific skin mast cell degranulation, suggesting implications for the pathogenesis of urticaria [11].

Considering that platelets may be activated during hypersensitivity reactions, inflammation, and infection and that platelets may contribute to pathogenesis of some types of urticaria, in the present study we measured plasma concentrations of PF-4, in order to clarify whether AU, presumably caused by infectious agents, is accompanied by increased secretory activity of circulating platelets. Moreover, we measured plasma concentration of C-reactive protein (CRP) and investigated possible relationships occurring between CRP and PF-4.

Material and Methods

We investigated 8 untreated patients (2 men and 6 women, the median age: 25.5 years) with generalized AU, presumably caused by infection, and 15 age- and sex-matched healthy controls. All patients suffered from clinically manifested acute respiratory tract infection, had never experienced any urticaria before, and did not take any drugs prior to AU onset. In addition, two patients had positive personal history for atopic diseases. No detailed laboratory tests were performed to identify possible etiology of the infectious diseases.

The Ethics Committee of the Medical University of Silesia approved of the study and written, informed consent was obtained from all the subjects participating.

Blood Sampling and PF-4 Measurement

Blood samples were obtained in the morning (7.00 a.m. to 8.00 a.m.; in the fasting state) after 25-minute rest at slight or no stasis from the antecubital vein into Diatube® H tubes (Becton Dickinson) then immediately placed in ice/water bath for 20 minutes. The tubes were then centrifuged at 2 500 g for 30 minutes at 4°C, and platelet poor plasma fractions were collected and frozen at –60°C until assay (not longer than 1 month). Plasma concentration of PF-4 was measured by enzyme-linked immunosorbent assay (ELISA), using commercial Asserachrom® kit by Diagnostica Stago, Paris, France.

Assay of CRP

Plasma concentration of CRP was evaluated using high sensitive immunoturbidimetric assay (COBAS INTEGRA C-reactive protein (Latex); Roche Diagnostics, Mannheim – Germany).

Statistical Analysis

Data are presented as medians with maximum and minimum values (range). Comparisons between groups were performed by Mann-Whitney's unpaired rank sum test. Correlation coefficient was obtained by Spearman test. *P* values lower than 0.05 were considered significant.

Results

In AU patients, PF-4 plasma concentration did not differ significantly from healthy controls. Patients with AU showed significantly increased CRP plasma concentration as compared with healthy subjects (Table 1). Moreover, no significant correlation was found between plasma con-

Table 1. PF-4 and CRP plasma concentration in patients suffering from acute infectious urticaria and in healthy controls

Tabela 1. Stężenie PF-4 i CRP w osoczu chorych na ostrą pokrzywkę w wyniku infekcji dróg oddechowych i w grupie kontrolnej

Analysed parameters (unit) (Badane wskaźniki – jednostki)	Healthy controls (Grupa kontrolna) n = 15 median range (mediana zakres)	AU patients (Chorzy na ostrą porzywkę) n = 8 median range (mediana zakres)	Statistical analysis (Analiza statystyczna) p
PF4 (IU/ml)	2.00 0.25–5.0	3.35 1.5–4.5	0.052
CRP (mg/l)	0.6 0.15–2.6	5.0 0.5–18.4	0.005

n – number of subjects, AU – acute urticaria; CRP – C-reactive protein; PF-4 – platelet factor 4.

n – liczba pacjentów, AU – ostra pokrzywka; CRP – białko C-reaktywne; PF-4 – czynnik płytkowy 4.

centration of PF-4 and CRP in AU patients (r = 0.48; P = 0.233). Neither were there any significant differences in peripheral platelet counts between the patients and the control subjects (data not included).

Discussion

It has been reported that platelet activation may occur in patients suffering from some forms of urticaria, such as cold urticaria [12] and cold urticaria accompanied by vasculitis [13]. However, literature discussing platelet activity in cold urticaria has appeared controversial. While one study has shown that platelets are activated in cold urticaria, suggesting that platelets are directly involved in the disease [12], other authors failed to find any significant differences in PF-4 circulating concentration following cold stimulus [14]. Hyperactivity of platelets, as detected by increased plasma concentrations of PF-4 and beta-thromboglobulin, has not been observed in patients with chronic idiopathic urticaria [15]. To the best our knowledge, there are no data on blood concentrations of the platelet-derived chemokines in patients with acute urticaria. Therefore, the intention of the present study was to extend our view of platelet function in this form of urticaria, presumably caused by infectious agents and to investigate possible relationships between CRP and platelet secretory activity, measured by plasma PF-4. There were no significant differences in plasma concentrations of PF-4 between AU patients and healthy subjects. However, PF-4 tended to be higher in the patients group (p = 0.052). Plasma CRP concentration was significantly higher in AU patients in the course of acute respiratory tract infection than in the controls.

It is known, that conditions imposing changes in plasma concentrations of acute-phase proteins include infections and various immunologically mediated inflammatory processes [16]. It seems likely that CRP plays numerous pathophysiological functions in the inflammatory reactions [16]. Interestingly, it has been suggested that CRP is an important factor to control platelet responsiveness to a variety of stimuli, during acute inflammatory reaction [17]. CRP inhibited platelet reactivities, include release mediators, stimulated by different factors [17].

Therefore, a speculative explanation of the results presented is that increased platelet secretory activity does not occur in the systemic circulation of AU patients presumably induced by acute infection, because platelet release reaction might be inhibited by CRP. On the other hand, no association between circulating concentrations of PF-4 and CRP has been proved for our patients. Potential limitation of the study performed was a small number of subjects evaluated and no identification of probable etiologies of the infectious diseases in our patients.

In conclusion, as compared to healthy subjects, patients suffering from acute urticaria in the course of acute infection of respiratory tract did not show significant differences in PF-4 plasma concentration, suggesting that acute urticaria, presumably induced by an infectious agent, may not prove accompanied by activation of circulating platelets effecting in the increased release of platelet-derived chemokine. Obviously, this does not exclude possibility of some changes in platelet activity and reactivity. If such activity occurs in the patients described should be determined employing other research methods.

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