Acute Phase Reactants in Allergic Airway Disease

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BÜYÜKÖZTÜRK, S., GELİNCİK, A.A., GENÇ, S., KOÇAK, H., ÖNERİYİDOĞAN, Y., ERDEN, S., DAL, M. and ÇOLAKOĞLU, B. *Acute Phase Reactants in Allergic Airway Disease*. Tohoku J. Exp. Med., 2004, **204** (3), 209-213 — Acute phase reactants have been implicated for their involvement as proinflammatory molecules in various inflammatory diseases. However, little is known regarding their role in the allergic airway disease. The aim of the present study was to examine the blood concentrations of three acute-phase proteins, namely C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen in patients with allergic rhinitis and asthma. Three study groups include: non-smoker allergic rhinitis ($n = 50$), non-smoker asthma ($n = 20$), and non-allergic, non-smoker healthy control subjects ($n = 20$). Patients who have had recent upper or lower respiratory tract infection and trauma, any rheumatological illnesses, malignancy or obesity were excluded. Blood samples were obtained from all the patients and control subjects and were analyzed for serum CRP, SAA and plasma fibrinogen. The mean CRP and fibrinogen values in the rhinitis and asthma groups were not significantly different when compared to the control group. However, the mean SAA levels of both groups were found to be significantly higher than those of the control group ($p = 0.002$ for rhinitis, $p = 0.02$ for asthma). There was no significant correlation between the FEV₁ values and the levels of the serum markers. This study demonstrates that acute phase reactant SAA rises in patients with allergic rhinitis and patients with asthma. We therefore suggest that SAA may have a role in the inflammatory airway disease. ——— acute phase proteins; C-reactive protein; Serum amyloid A; fibrinogen; allergic rhinitis; asthma; inflammation

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Several acute phase proteins have been mentioned to be substantially elevated during infection, trauma, surgery, burns, tissue infarction, various immunologically mediated conditions or cancer (Gabay and Kushner 1999). As their changes reflect the presence and intensity of in-

flammation, they have been used as clinical markers in the diagnosis and management of some diseases. However, recent evidence has suggested that some of them might have proinflammatory properties (Blake and Ridker 2001). C-reactive protein (CRP), which is one of the most common-

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ly studied acute phase proteins, is shown to stimulate the release of inflammatory cytokines in monocytes. Another major acute-phase protein, serum amyloid A (SAA) is also demonstrated to cause adhesion and chemotaxis of phagocytic cells and lymphocytes in atherosclerotic plaques.

Asthma is considered as an inflammatory disease of airways. According to recent data, asthma and rhinitis are closely linked entities and they together define the unique inflammatory disorder, "United Airway Disease" (Passalacqua and Canonica 2002), or "Combined Allergic Rhinitis Asthma Syndrome." Some inflammatory markers, such as eosinophils, interleukin-5 (IL-5), eotaxin, eosinophilic cationic protein (ECP), and nitric oxide (NO) have been used to demonstrate the presence and persistence of airway inflammation.

In present study, we aimed to investigate the serum and plasma concentrations of three acute phase proteins, CRP, fibrinogen and SAA, in patients with allergic rhinitis and with asthma.

MATERIALS AND METHODS

Among patients who referred to our out-patient clinic between September 2003 - December 2003, 50 consecutive patients with perennial allergic rhinitis and 20 with asthma have been chosen as the study groups. The diagnosis of rhinitis and asthma has been based on the history, physical examination, nasal smears, skin prick tests, paranasal sinus computerized tomographies (CT), pulmonary function tests with reversibility detection and chest x-rays. Exclusion criteria included a recent upper or lower respiratory tract infection and trauma, a rheumatological illness, malignancy and obesity. The patients whose sinus CT revealed prominent sinusitis, those who were on corticosteroid therapy and current smokers were also excluded. Twenty non-smoker healthy subjects with similar ages and female/male ratio consisted the control group.

After taking the informed consents of the patients, blood samples of 10 ml have been obtained in appropriate conditions. All the asthmatic and allergic rhinitis patients were in asymptomatic

stages when the blood samples were drawn. The samples were stored at -70°C until the day on which they were analysed for the concentrations of three inflammatory markers.

Serum CRP concentrations were determined by microparticle enhanced turbidimetry with clinical chemistry analyzer Cobas Integra 400 (Roche Diagnostics GmbH, Mannheim, Germany). Reference value by the clinical laboratory was < 5 mg/100 ml. Serum amyloid A concentration was measured using a Sandwich enzyme immunoassay kit (Biosource Int. Inc., Camarillo, CA, USA). Normal serum levels of SAA are < 10 $\mu\text{g/ml}$, as suggested by Thomas (1982). Plasma fibrinogen was measured using coagulometric techniques (Behring Coagulation Timer). The levels of each inflammatory marker were compared between the study groups and the control group, using SPSS 10.0 version. In addition, the patients were compared in regard to disease severity as reflected by symptom levels and FEV_1 values. Statistical analysis between the three groups was done by Kruskal-Wallis test. Pearson test was used for correlation analysis.

The study has been approved by the ethics committee of Istanbul University Faculty of Medicine.

RESULTS

In the rhinitis and asthma groups, there were great differences in the CRP (0.44-44.92 mg/100 ml) and SAA (9.59-932 $\mu\text{g/ml}$) concentrations of patients in contrast to fibrinogen, which was rather stable (Table 1). Although very high CRP levels were noticed in patients with rhinitis and asthma, the mean CRP and fibrinogen values in these groups were not significantly different when compared to the control group. However, the mean SAA levels of both groups were found to be significantly higher than that of the control group ($p = 0.002$, $p = 0.02$ respectively). As the allergic rhinitis and asthma have been regarded to be close entities by most authors, the two patient groups were combined as one and similar results were obtained when compared to the control group ($p =$

TABLE 1. *The comparison of the characteristics of three groups[§].*

	Allergic rhinitis <i>n</i> = 50	Asthma <i>n</i> = 20	Control group <i>n</i> = 20	Significance	
				* <i>p</i>	** <i>p</i>
Age	18-43 (mean 32)	18-49 (mean 36)	17-36 (mean 31)	NS	NS
Gender (F/M)	36/14	14/6	15/7		
FEV ₁ (%predicted) [†]	92 (± 12.6)	88 (± 11.4)	102 (± 6.4)	NS	< 0.05
CRP mg/100 ml	4.2 (± 8.8)	3.06 (± 2.7)	3.3 (± 6.4)	NS	NS
Fibrinogen mg/ml	3.4 (± 1.3)	3.5 (± 1.3)	2.8 (± 0.5)	NS	NS
SAA µg/ml	71.7 (± 158)	66.3 (± 74.7)	19.5 (± 1.8)	<i>p</i> = 0.002, <i>p</i> = 0.02	

* Rhinitis vs. control.

** Asthma vs. control.

[†] FEV₁ = forced expiratory volume in 1st second, expressed as % of predicted value.[§] The values are expressed as mean ± s.d.

0.009). No significant correlation was found between the serum markers and FEV₁ values.

DISCUSSION

The results of the present study demonstrate that SAA concentrations are higher in patients with asthma and allergic rhinitis. This was not associated with any other inflammatory status of the patients and was not correlated with disease severity as reflected by FEV₁ values. So far, we have been able to find only one study investigating the association of SAA with bronchial asthma. Jousilahti et al. (2002) have reported in their cross-sectional population-based study that SAA and fibrinogen were positively associated with asthma prevalence and they had concluded that systemic inflammation also existed besides the local inflammation in bronchial asthma. In two previously published population-based studies, high fibrinogen levels had been observed in asthmatic patients (Enright et al. 1996) and in chronic obstructive pulmonary disease (COPD) (Dahl et al. 2001).

Serum amyloid A has been mentioned to be an important acute phase reactant whose level in the blood increases in response to various insults (Urieli-Shoval et al. 2000). Its synthesis has been demonstrated to be regulated mainly by IL-1, TNF- α , IL-6 and glucocorticoids at both the transcriptional and post-transcriptional levels (Jensen

and Whitehead 1998). Although its physiological role is not fully understood, it has been proposed by various studies that it involves in cholesterol metabolism and transport and in modulating the inflammatory response via both anti- and proinflammatory activities (Urieli-Shoval et al. 2000). SAA is implicated for its role in the pathogenesis of atherosclerotic plaques (Meek et al. 1994) and is detected in the brains of Alzheimer patients. Urieli et al. (1998) demonstrated SAA expression in histologically normal human tissues, mainly in epithelial and endothelial cells, and in lymphocytes. SAA has been demonstrated to be elevated in patients with lung cancer (Benson et al. 1986; Howard et al. 2003), cystic fibrosis (Smith et al. 1992), pulmonary tuberculosis (DeBeer et al. 1984) and sarcoidosis (Rothkrantz-Kos et al. 2003).

Allergic rhinitis and asthma are considered to be the two entities of the atopic syndrome (Braunstahl et al. 2003). Allergic rhinitis is also suggested to be related to systemic allergic manifestations. One of the proofs of this hypothesis is the systemic circulation of IgE antibodies, and another is peripheral eosinophilia (Alkis and Togias 2000). Different studies have indicated the involvement of the bone marrow in the development of eosinophilic inflammation of the airways. Denburg et al. (2000) have proposed that "the bone marrow is an ongoing source of chron-

ic, systemic inflammation that seeds atopic tissues with cells that are capable of maturing into the effector cells of allergy”.

Taken all together, we conclude that elevated SAA concentrations in patients with allergic airway disease may indicate the presence of systemic inflammation. The role of SAA in the airway inflammation still remains to be elucidated. Recently, Kallapur et al. (2003) demonstrated SAA 3 mRNA expression in the bronchial epithelial cells of the preterm lambs, due to endotoxin-induced lung inflammation. Accordingly, it could be argued that SAA could be produced in the bronchial epithelial cells in response to airway inflammation in rhinitis and asthma. Obviously, the issue whether SAA can be useful for the follow-up of the allergic airway disease requires future investigations.

In conclusion, we found higher SAA concentrations in patients with allergic rhinitis and those with asthma compared to the control subjects. We suggest the involvement of SAA in development or persistence of these diseases.

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