Original Article

Renin angiotensin aldosterone system in anaphylactic reactions induced by immunotherapy

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ABSTRACT

Although patients with a history of hymenoptera venom anaphylaxis showed significantly reduced plasma levels of angiotensin-I and angiotensin-II compared to controls, there is no study in the literature to investigate the renin angiotensin aldosterone system (RAAS) in patients with anaphylactic reaction induced by immunotherapy. The purpose of this study is to determine the role of the renin angiotensin aldosterone system in patients who had an anaphylactic reaction induced by allergen immunotherapy with pollen, house-dust and mold extracts. Plasma levels of angiotensin-I, angiotensin-II, angiotensin converting enzyme and aldosterone were measured in 20 patients who experienced anaphylaxis during allergen immunotherapy. The control group consisted of 15 immunotherapy patients without any history of anaphylaxis. The Mann–Whitney U-test was performed for comparison of the two groups, and a P value less than 0.05 was considered statistically significant. Angiotensin-I, angiotensin-II, angiotensin converting enzyme and aldosterone levels were similar in both the study and control groups and no statistical significance was found between the two groups (P > 0.05). The RAAS does not appear to play a role in the pathogenesis of anaphylactic reactions due to allergen immunotherapy with pollen, house-dust and mold extracts.

Key words: anaphylaxis, immunotherapy, renin angiotensin system.

INTRODUCTION

Acute anaphylaxis is a potentially life-threatening clinical picture. Mast cells and basophils, which are activated by immunoglobulin E (IgE) and allergen, play a prominent role in these reactions. However, recent studies have shown that non-immunologic factors, such as renin angiotensin aldosterone system (RAAS), may play a role in the pathophysiology of the anaphylactic reactions. The role of the RAAS in cardiovascular function and disease has long been recognized. The RAAS acts systemically and locally to influence vascular tone, blood volume and myocardial contractility. It is also an important back-up mechanism for maintaining arterial blood pressure during circulatory challenges.1 Patients with a history of anaphylactic reactions induced by bee or wasp venom showed significantly reduced serum angiotensin-I (A-I) and angiotensin-II (A-II) levels compared to controls.2–4

In this study, we investigated the role of the RAAS in the anaphylactic reactions triggered by allergen immunotherapy with pollen, house-dust and mold extracts.

PATIENTS AND METHODS

The study was carried out at the Department of Allergy at the Gülhane Military Medical Academy in Ankara, Turkey and consisted of 20 patients (13 males, 7 females) with allergic rhinitis and bronchial asthma. All patients had experienced severe anaphylaxis during the build-up period of allergen immunotherapy with aqueous extracts of aero-allergens. The control group consisted of 15 sex, age and diagnosis matched immunotherapy patients (10 males, 5 females) without a history of anaphylaxis.
Serum levels of A-I, A-II, angiotensin converting enzyme (ACE) and aldosterone were measured in both groups. Venous blood was withdrawn soon after the anaphylaxis from a cubital vein directly into a plain glass tube. The serum samples were frozen at –70°C until the tests were performed.

The radio-immunoassay method was used to measure A-I (SORIN Biomedica, Saluggia-Vercelli, Italy), A-II (EURO Diagnostic B.V., Arnhem, Holland) and aldosterone (Diagnostic System Laboratories Inc., Texas, USA) levels.

Statistical analysis was performed using the Mann–Whitney U-test with SPSS/PC (Statistical Program for the Social Sciences, Version 6.00). A P value less than 0.05 was considered statistically significant.

## RESULTS

Mean age was 27.45 ± 2.06 years in the study group and 29.27 ± 2.23 years in control group. Results of the study and control group are presented in Table 1.

The A-I, A-II, ACE and aldosterone levels were similar in both groups and the difference between the two groups was not statistically significant (P > 0.05). (Table 2.)

## DISCUSSION

Circulation has several protective mechanisms which maintain perfusion of vital organs in the event of an acute hypotensive episode. Regulation of these circulatory responses is provided by the integrated effects of
both neural and hormonal systems. The sympathetic nervous system and the RAAS are the most extensively studied systems. The RAAS was first recognized as a classical endocrine system with effects mediated entirely by circulating hormones. However, it has been recently demonstrated that all components of the system are present in many tissues.\textsuperscript{5,6}

Hermann and co-workers reported that the plasma concentrations of all components of the RAAS are reduced in patients with a history of anaphylactic reactions to hymenoptera venom. Likewise, A-II concentrations in their leukocytes were significantly reduced and a significant correlation between the severity of clinical symptoms and the A-II levels was found. These findings suggested that the renin-angiotensin system may play an important role as a counteracting factor in hymenoptera venom anaphylaxis.\textsuperscript{4,7–9}

It is well known that the major risk of allergen immunotherapy is the development of a systemic anaphylactic reaction. Factors determining the risk of an allergic response are not fully understood. Although immunologic factors are important, non-immunologic factors such as a defect in the circulating RAAS, may also play a role in the pathogenesis of anaphylaxis. The impaired activity of the RAAS may contribute to the dramatic fall in blood pressure in anaphylactic shock. Whether this is confined to anaphylaxis resulting from hymenoptera stings, or is a feature of other forms of anaphylaxis, remains unclear.\textsuperscript{6}

Advanced studies have shown that in patients with successful immunotherapy who tolerated the sting of a living insect, renin, A-I and A-II were significantly higher than in patients without immunotherapy. After immunotherapy, the levels of renin, A-I and A-II were similar to those found in healthy nonallergic controls.\textsuperscript{10} The reversal of the defect after hyposensitization indicates an acquired phenomenon, perhaps with an immunologic origin. Cross-reactivity of antibodies to hymenoptera venom and angiotensinogen may be one possible explanation.\textsuperscript{6} In addition, it has been found in animal studies that the passive transfer of antibodies to angiotensinogen also decreases plasma renin activity despite a reduction in blood pressure.\textsuperscript{11}

Our study group consisted of patients with allergic rhinitis and bronchial asthma who were sensitive to house dusts, pollens and molds. Anaphylactic reactions occurred in the early phase (build-up period) of immunotherapy. The A-I, A-II, ACE and aldosterone levels were found within normal ranges soon after anaphylaxis. There was no statistically significant difference between the study group and the controls (P > 0.05). Although Hermann and Ring reported reduced plasma levels of RAAS components in their patients with anaphylactic reactions to hymenoptera venom, we did not find any difference in angiotensin II levels between patients with immunotherapy-induced anaphylactic reactions and the control group.\textsuperscript{2,3} In another study, decreased levels of angiotensin II in white blood cells of patients with anaphylactic reactions to hymenoptera venom was reported. In addition, it has also been demonstrated that decreased levels of angiotensin II have a close relationship with the severity of the symptoms.

A number of studies have reported that all patients have anaphylactic reactions to hymenoptera venom; however, other factors leading to anaphylactic reactions have not been considered in these studies. There may be a close relationship between anaphylactic reactions to hymenoptera venom and angiotensin II, as pointed out in these studies. In fact, a cross-reactivity between antibody to hymenoptera venom and angiotensin has been suggested. After making a decision for the relationship between the RAAS and anaphylactic reactions to hymenoptera venom, the relationship among other anaphylactic reactions and the RAAS become more important in explaining the pathophysiology of these types of reactions. Although an elevation of angiotensin II levels in patients with acute severe asthma has been shown in some studies, we did not find any difference between asthmatic patients who had shown immunotherapy-induced anaphylactic reactions and the control group. The RAAS is activated in acute severe asthma, although not in all asthmatics. The mechanism of this activation is unclear, but recent evidence has shown elevation of renin and angiotensin II in response to nebulized and intravenous salbutamol.\textsuperscript{12,13}

It can be seen that this phenomenon may be confined to only hymenoptera venom sensitive patients. However, further studies should be planned to fully define the responsiveness of the RAAS in sensitized subjects.

\textbf{References}


