

Table 1. Rate of asthma, allergic rhinitis, their association, and sensitization in outpatients during 1981 and 1995

	1981	1995	
Asthma	64	35	$P < 0.05$
Allergic rhinitis	82	70	NS
Asthma and allergic rhinitis	69	114	$P < 0.05$
Polysensitization	117	158	$P < 0.05$

positive skin prick test in agreement with history and clinical local examination (3, 4).

We implemented our studies with the same criteria to establish the diagnosis of asthma and allergic rhinitis as well as to perform the skin prick test.

The skin prick test was performed on all subjects, according to methodology and criteria proposed by the Italian Society of Allergy and Clinical Immunology (5), and with a common panel of allergens (3, 4). Sensitization was considered when there was a relationship between history and skin prick test positivity (i.e., wheal diameter ≥ 3 mm). Subjects with just one positive skin prick test were considered monosensitized; on the other hand, subjects with two or more positive skin prick tests were considered polysensitized. Statistical analysis was performed by the chi-square test, confidence limits of the relative risk being calculated at 95%.

The distribution of lifetime asthma and allergic rhinitis rates, and their association in 1981 and 1995, respectively, are shown in Table 1. The prevalence of asthma was significantly decreased in the second observation ($P < 0.05$), while the prevalence of its association with rhinitis was increased ($P < 0.05$).

Polysensitized subjects significantly increased in 1995 in comparison with 1981 ($P < 0.05$).

Mite allergen appeared to be the most important causal allergen: mite cutaneous positivity increased ($P < 0.05$); there was an increase in polysensitized subjects ($P < 0.001$).

The pollen sensitization decreased in total ($P = 0.001$) and for monosensitized ($P < 0.009$) subjects.

Pet sensitization showed an increasing trend ($P < 0.05$); only one patient was monosensitized.

The most important finding of this study was the increasing trend of the association of asthma with allergic rhinitis over the period studied. This finding confirms the trend of a growing worsening of allergic diseases, and it is similar to that of our previous survey on conscripts (3).

Other findings of the present study show that indoor allergens are predominant in the present context and there is an increasing trend of polysensitizations. These findings are also consistent with the conscript observations (3).

In other words, it would seem that the epidemiologic role of allergic diseases is growing both as prevalence and spectrum of clinical features and

sensitizations. A possible explanation of these findings is the increasing pathogenetic role played by environmental factors (1). In fact, it is well known that allergic diseases are genetically influenced (1), but they appear clinically when aggressive factors break the immunologic equilibrium, allowing sensitization to occur (2). Among these factors, air pollution, viral infections, and changes in the indoor microenvironment (such as heating methods, thermal proofing devices, the introduction of pets, etc.) may play a critical role. In fact, this study suggests that indoor allergens are the major cause of allergic respiratory diseases, probably because they are perennial. In conclusion, it clearly appears that asthma and allergic rhinitis are two pathologic conditions causing increasing economic costs in terms of health care.

Key words: allergic rhinitis; asthma; epidemiology; polysensitization.

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Autoimmune vasculitis and aortic stenosis in aspirin-induced asthma (AIA)

ASPIRIN-induced asthma (AIA), a distinct clinical syndrome, affects about 10% of adult asthmatics. Attacks of asthma precipitated by aspirin are related to the inhibition of cyclooxygenase in the lungs of sensitive patients, and not

to the body's reaction to the allergen (aspirin) (1). Immunologic mechanisms may, however, become involved in the course of the disease (2-4). Recently, signs of autoimmunity have been observed (5, 6) in some patients with AIA. This prompted us to report the case here described.

A 46-year-old woman had been in good health until the age of 21, when she developed chronic watery rhinitis. Three years later, during pregnancy, dyspnea appeared, and bronchial asthma was diagnosed. Shortly afterward, she had an attack of asthma after taking aspirin. At the age of 29, she had a positive oral aspirin challenge test performed at our department. A nasal polyp was removed. Over the following 18 years, she was followed up closely by us. Her asthma was of moderate severity, requiring 5-15 mg prednisone/day to control the symptoms. It was characterized by normal serum IgE and blood (400-1500/mm³) and bronchoalveolar lavage fluid (2-7%) eosinophilia; the patient was negative to both skin tests and serum specific IgE to common aeroallergens. Pulmonary function tests showed mild reversible obstruction, while total lung capacity and diffusing capacity remained within the normal range. Chest radiographs showed no abnormalities.

Since adolescence, the patient's fingers had turned bluish when immersed in warm water; no pain occurred. At the age of 35 years, she developed hypertension, the cause of which could not be identified, and which remained well controlled with antihypertensive therapy. At the age of 38 years, her fingers and toes became permanently violet; livedo racemosa was noticed in her arms, legs, and back. On examination, her hands and toes were cool and cyanotic; her pulses were palpable. A superficial ulceration occupied the tip of a finger. Cooling of hands did not evoke Raynaud's phenomenon. Capillaroscopy revealed a normal number of capillaries, the central parts of which were distended and showed signs of stasis. On laser Doppler flowmetry, the flux motion waves were preserved, but flow was depressed through nutritional capillaries. Color Doppler revealed no gross abnormalities in the vascular system. Routine blood chemistry and urinalysis were normal. The serum homocysteine level was within normal range, and search for serum paraproteins gave negative results. Autoantibodies against ss-DNA were present at the titer 1:1280 in serum; their specificity could not be identified with reference sera against extractable nuclear antigens (Sm, U1RNP, SS-A, SS-B, Jo-1, Scl-70). Anti-ds-DNA, anticentromere, antineutrophil cytoplasmic antibodies (ANCA), and lupus anticoagulant and anticardiolipin antibodies were absent. There was no evidence of complement activation, rheumatoid factor, or circulating immune complexes. Skin

biopsy of the thigh was negative. In the differential diagnosis, polyarteritis nodosa and peripheral scleroderma were ruled out by clinical and laboratory examination.

At the age of 42 years, the patient started to experience chest pain on exertion, and an ejection systolic murmur became audible in the second right intercostal space. Echocardiography revealed a bicuspid aortic valve with a peak systolic pressure gradient of 35 mmHg. Over the next 3 years, fatigue and symptoms of angina pectoris increased; intermittent attacks of vertigo without syncope became prominent.

A woman with AIA and autoimmunity, pointing to an association between the two disorders.

Electrocardiography showed left ventricular hypertrophy, and the systolic pressure gradient reached 65 mmHg. An oral provocation test (1) with 80 mg aspirin was positive, ANCA at the titer 1:640 were present in serum, antiphospholipid antibodies were undetectable, the rheumatic symptoms were absent, and routine blood tests were normal. In 1996, at the age of 46 years, her aortic valve was successfully replaced. Histologic examination of the valve revealed signs of inflammation with fibrotic and sclerotic changes, local edema, and degeneration of collagen fibers. In these regions, as well as in and underneath the endocardium, distinct deposits of IgG, IgA, IgM, C3C, and fibrinogen were seen, indicating an active immunologic process affecting the valve.

In our patient, typical AIA coincided with vasculitis for at least 25 years. For many years, it was confined to distal parts of the body, but gradually occupied larger areas of skin, giving rise to pronounced livedo racemosa and ulcerations of the tips of fingers. Eventually, the patient developed rapidly progressing tight aortic stenosis. We considered the possibility that development of stenosis was preceded by valvular endocarditis that had an autoimmune background. Thus, histologic examination of the valve, removed at surgery, disclosed distinct signs of an active, immunologically mediated inflammatory process. The predisposing factor could have been a bicuspid valve, a relatively common aortic malformation. A bicuspid valve can itself lead to development of aortic stenosis in middle age. However, in contrast to findings in our patient, marked calcification is always present, while signs of active immunologic process are absent (7).

Clinical signs of autoimmunity have only sporadically been reported in patients with AIA (8, 9), and clearly are not among the major symptoms of

the AIA syndrome. Nevertheless, 55% of AIA patients have antinuclear antibodies at a low titer present in serum, and 6% of all aspirin-intolerant asthmatics have evident clinical signs of autoimmune disease (6). Lassalle et al. (5) described circulating IgG autoantibodies directed against a common 55-kDa antigen shared by platelets and endothelial cells in 34/97 asthmatic patients, many of whom had AIA. Our report adds to recent observations indicating the association of autoimmune phenomena with AIA. Assessment for autoimmunity might help to characterize patients with asthma and to implement the appropriate therapy.

Key words: aspirin; aspirin-induced asthma; autoimmunity; vasculitis.

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Angioedema of ACE inhibitors

ANGIOEDEMA, although generally mild, can be a life-threatening adverse effect of angiotensin-converting enzyme inhibitors (ACEIs) (e.g., benazepril, captopril, cilazapril, enalapril, fosinopril,

lisinopril, perindopril, quinapril, and ramipril) (1). The exact mechanism of ACEI-mediated angioedema remains unclear, but bradykinin has been implicated in its pathogenesis (2). ACEIs not only block the conversion of angiotensin I to angiotensin II, but also inhibit the degradation of bradykinin (3), a potent activator of the L-arginine nitric oxide system that causes vasodilation, increases vascular permeability, and also produces hypotension. We present a patient with ACEI-mediated angioedema, and re-emphasize the possible contraindications to their administration.

■ A 69-year-old woman was referred to our department because of an episode of precipitous tongue swelling with stridor and dyspnea. Her history revealed no atopic background and she had no antecedents of drug or food allergies. However, she recalled two similar though less severe reactions. Review of her medical record revealed, on several occasions, a coincident occurrence

A case of angioedema mediated by angiotensin-converting enzyme inhibitors has initiated a discussion of potential contraindications.

of angioedema with the initiation of an ACEI, i.e., captopril (Capoten®), fosinopril (Fosinil®), and quinapril (Accupril®). Serum complement determinations revealed a total hemolytic complement (CH50) of 267 U/ml (range, 133-243), C4 of 31 mg/dl (range, 14-56), C3 of 166 mg/dl (range, 69-177), C3d of 0.17 mg/dl (normal <0.38), a functional C1-esterase inhibitor activity of 120% (range, 60-150), and a quantitative C1-esterase inhibitor level of 32 mg/dl (range, 0.15-0.35). A lymphocyte transformation test for enalapril, skin prick tests for classical food and inhalant allergens, and the test for enalapril up to an undiluted end-point concentration were negative.

■ This case exemplifies recurrent ACEI-dependent angioedema appearing within the first week after initiation of different ACEIs. The reaction is usually mild and characterized by well-demarcated, nonpruritic, and nonpitting swelling of the face, eyelids, lips, tongue, and oropharynx with dysphagia, or, in rare cases, by edema of the gastrointestinal tract. Generally, it subsides within hours after cessation of the intake of the inciting drug. However, progression to upper airway (larynx) obstruction with stridor, respiratory distress, and death has been reported (1). Urticaria is rarely observed. ACEI angioedema can occur with chemically unrelated

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