

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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Accepted for publication 2 January 1997  
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ALLERGY 1997;52:352-354

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## Angioedema of ACE inhibitors

**A**NGIOEDEMA, 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

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

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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

ACEIs in the same patient, and seems to be dose-independent. In postmarketing surveillance studies, the overall incidence of ACEI-associated angioedema approximated 0.1–0.2% and was found to be more common in Afro-Americans. As in our patient, the time of onset is usually within hours or, at most, the first days of administration (1); however, reports of delayed-onset angioedema occurring months to years after initiation of the drug have been published (1). Evidence has emerged that interruptions of the ACEI treatment may represent a possible risk factor for late-onset ACEI angioedema. Though the exact pathogenesis of ACEI-mediated angioedema remains unknown, the nonapeptide bradykinin appears to play a key role. Bradykinin, cleaved from high-molecular-weight kininogens by kallikrein, is a potent activator of the L-arginine nitric oxide system that causes vasodilation and increases capillary leakage (4).

Normally, ACE (i.e., kininase II), by releasing the carboxy-terminal dipeptide Phe-Arg, rapidly inactivates bradykinin and related kinins. Bradykinin accumulation and/or potentiation – as a consequence of kininase II inhibition (3) – has been implicated in the pathogenesis of ACEI-associated angioedema (2), especially when bradykinin generation is enhanced. We have observed a man with a quantitative hereditary C1-esterase inhibitor deficiency, a condition characterized by enhanced bradykinin generation, who suffered from severe anaphylactoid reactions precipitated by the oral and intravenous administration of different ACEIs (5). In fact, pre-existing angioedema should be a contraindication for the use of an ACEI. Recently, Boxer (6) reported a 58-year-old man with angioedema after the separate use of both quinapril (Accupril®) and losartan (Cozaar®). The latter belongs to the orally active angiotensin II receptor antagonists, which do not affect bradykinin degradation.

In conclusion, angioedema, probably due to an accumulation of bradykinin, can be a potentially life-threatening adverse effect of ACEI, especially in patients with pre-existing angioedema. If, by careful questioning of the patient, ACEI-associated angioedema is suspected, the inciting drug should be stopped promptly.

Key words: angioedema; angiotensin-converting enzyme inhibitor (ACEI); bradykinin; losartan.

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Accepted for publication 7 January 1997

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ALLERGY 1997;52:354–355

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## Cypress allergy: an underestimated pollinosis

CYPRESS pollen allergy has been reported to cause winter conjunctivitis, rhinitis, and asthma. The clinical picture of this pollinosis, characterized by symptoms often mimicking those of "recurrent" viral infections, could contribute to the underevaluation of the importance of the pollen from the Cupressaceae family as a cause of allergic symptoms.

In order to determine whether a correct diagnosis of cypress allergy can be concealed by a wrong one of a generic winter respiratory disease (common cold, influenza syndrome, etc.), we conducted a 4-year study on 1393 patients, with the collaborative support of the general practitioners of the national health service, in a central region of Italy. The subcontinental climate of the region allows Cupressaceae to pollinate in winter, while grass, olive, and *Parietaria* pollen

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*This 4-year prospective clinical study indicates that cypress allergy is often mistaken for viral infection.*

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are present from the end of April to the end of June. All the patients had consulted their own family physician before referral to the allergy department. They numbered 303 in 1991, 371 in 1992, 355 in 1993, and 364 in 1994. Clinical history was based on self-reported symptoms and diagnostic indications by the family physician. The patients were then skin-prick-tested with a panel of diagnostic extracts by a standard procedure (1).

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