

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

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

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).

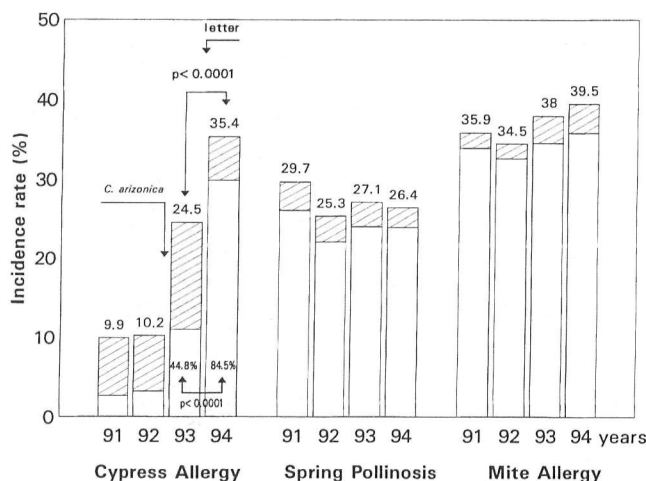


FIGURE 1 Incidence of clinically relevant diagnosis (1991–4). Comparison of cypress pollinosis, spring pollinosis, and mite allergy. On each bar is indicated rate of “SPT-addressed diagnosis” (hatched part) vs “family physician-addressed diagnosis” (white part).

For the purpose of this study, only the results of skin prick test (SPT) with cypress, mites, and spring pollens (grass, olive, and pellitory) were considered. *Cupressus sempervirens* extract (Bayer, Milan, Italy) was used from 1991 to 1994. At the beginning of 1993, a characterized extract of *C. arizonica* (2) was added to the panel of allergens. After the SPT results were obtained, the patient clinical history was matched with the results of SPT itself and analyzed for the presence of any correlation between self-reported symptoms and SPT results. The positive patient history and a following positive SPT diagnosis were regarded as "family physician-addressed diagnosis". The absence of clinical relevance of SPT-positive results was carefully reassessed by an exhaustive interview of the patient; in a limited number of subjects, a follow-up was necessary. If SPT positivity without clinical symptoms was still recorded, it was scored as preclinical allergy and not considered in this study. If clinical relevance of SPT positivity was recorded, it was scored as "SPT-addressed diagnosis". At the beginning of January 1994, we sent a letter to the general practitioners of the national health service, stressing the elements useful for differential diagnosis, and wintertime recurrent rhinitis nonresponsive to anti-phlogistic-antibiotic therapy proved to be the clinical picture most frequently suggesting cypress allergy.

The incidence of a new clinically relevant diagnosis, reported as percentage of all the new patients seen in a year, is reported in Fig. 1. No statistical difference in this parameter was recorded for spring pollinosis and for mites in the 4 years. A low

incidence of cypress allergy diagnosis, without a statistically significant difference, was recorded in 1991 and 1992 (9.9% and 10.2%, respectively). The use of the characterized *C. arizonica* pollen extract caused an increase in the overall number of new diagnoses in 1993 (24.1%). A further increase was recorded in 1994 (35.4%) after the communication was sent. Both these rates were statistically significant (chi-square test $P < 0.0001$) when compared with the previous year.

The rate of the "family physician-addressed diagnosis" was very high and without statistically significant variation in both the group with spring pollinosis and that with mite allergy (Fig. 1). A progressive shift from "SPT-addressed diagnosis" to "family physician-addressed diagnosis" was recorded in the group with cypress allergy. The rate of the former decreased in the period 1991–3 but without significant variation. A highly significant increase (up to 84.5%) of the latter was recorded in 1994 (Fisher's exact test $P < 0.0001$) (Fig. 1).

The lack of a characterized allergenic extract to use in the *in vivo* or *in vitro* diagnosis of cypress allergy is the first cause of a false low prevalence of this pollinosis (1). However, the onset of this allergic respiratory disease as a seasonal infective respiratory disorder is responsible for its clinical under-evaluation. Improving the knowledge of the clinical and diagnostic features of cypress pollinosis will avoid a wrong diagnosis followed by an unsuccessful therapy. Furthermore, the use of a characterized extract from higher cross-reacting species (1, 3) will help exclude a false-negative diagnosis.

Key words: Cupressaceae; cypress; diagnosis; winter pollinosis.

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Accepted for publication 18 December 1996

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ALLERGY 1997;52:355-356

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