



Letters

Treatment of idiopathic nonhistaminergic angioedema with bradykinin B2 receptor antagonist icatibant

Idiopathic nonhistaminergic form of angioedema (AE) is a potentially life-threatening condition. It is characterized by local swelling involving the deeper dermis and subcutaneous tissue and results from the release of mediators that cause vasodilatation and enhanced capillary permeability. Normal C1 inhibitor (INH) antigenic levels and function and normal C4 levels are the hallmark.¹ Up to now, epidemiological studies on this form of AE are missing, and the frequency in the general population is unknown. The clinical features of this form are similar to those of hereditary AE (HAE) and acquired C1 INH deficiency. Pathophysiological evidence suggests that bradykinin is involved in HAE, in angiotensin-converting enzyme (ACE) inhibitor-induced AE, and in idiopathic nonhistaminergic AE, whereas bradykinin is not involved in allergen-dependent or idiopathic histaminergic AE that is responsive to antihistamines. The synthetic decapeptide icatibant, a selective competitive antagonist at the bradykinin B2 receptor, is authorized in Europe for the treatment of acute attacks of HAE.^{2,3} Recently, its successful use in severe ACE inhibitor-induced AE has been described.⁴ Its mechanism of action makes icatibant a promising drug for the idiopathic nonhistaminergic form of AE. We describe here its successful use in this condition, in which pharmacological treatment with antihistamines, corticosteroids, and epinephrine is often poorly effective.¹

A 48-year-old white man was admitted to the Clinical Immunology Unit, Department of Internal Medicine, University of Pisa, for recurrent episodes of AE of the face and neck involving the tongue and larynx, dating from 1993. An extensive clinical and serological workup was performed. Normal INH antigenic levels and function and normal C4 levels were detected, and other potential causes of AE were excluded. Family history of AE was not reported. Before admission to our Unit, hypersensitivity to benzoate was diagnosed, but a specific diet avoiding this substance for 2 years did not improve the frequency and the intensity of AE episodes. The AE worsened despite different pharmacological treatments for long-term prophylaxis (including sedating oral H1 antihistamines, nonsedating oral H1 antihistamines at off-label doses, tranexamic acid, corticosteroids, anti-leukotrienes, cyclosporine, and colchicine). For the severity and frequency (1–2 episodes/month) of larynx AE attacks, the patient was often admitted to the Emergency Unit, where he received treatment with high doses of intravenous methylprednisolone or hydrocortisone and chlorpheniramine maleate. Despite these treatments, the patient developed laryngeal AE requiring inhaled and intravenous epinephrine to obtain remission of laryngeal AE. Because of the potential severe adverse effects of epinephrine and high doses of corticosteroids, we

decided to treat the patient with a 30-mg subcutaneous dose of icatibant and intravenous corticosteroids. Written informed consent was obtained from the patient for this off-label use. After the icatibant injection, the patient experienced an arrest of the progression of AE attacks without development of laryngeal AE within 10 minutes and its complete resolution within 3 hours. Subsequently, every episode (1 episode/month for a total of 6 attacks) of AE was treated successfully with subcutaneous icatibant. The patient is self-administering the drug at the beginning of each attack, and in 2 episodes he needed a second dose of icatibant 30 mg after 6 hours from the first one to obtain a complete remission of the AE.

Antihistamines remain the first-line treatment for idiopathic AE; a number of drugs, including dapson, methotrexate, cyclosporine, sulfasalazine, and colchicine, have been reported to be beneficial. However, alternative therapeutic approaches are often required in those patients with idiopathic AE that does not respond to traditional treatments. Recently, the successful use of rituximab, a B-cell-depleting monoclonal anti-CD20 antibody, has demonstrated potential benefit in idiopathic AE.⁵

In our patient, unresponsive to high doses of antihistamines, the involvement of histamine as the mediator of AE appears unlikely. Although we do not have direct evidence of a bradykinin-mediated pathogenesis, the complete response to icatibant strongly suggests the crucial role of bradykinin. Our observation indicates the potential benefit of icatibant not only in HAE and ACE inhibitor-induced AE, but also in those potentially life-threatening forms of acute AE of unknown pathogenesis in which bradykinin is suspected to be the mediator of swelling. Moreover, the successful response to icatibant treatment may allow the correct classification of an idiopathic nonhistaminergic AE as probably bradykinin-mediated.

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Eutamias sibiricus: a new pet as a cause of asthma

The effects of pet exposure on the development of respiratory symptoms have become an increasingly common problem. Allergic diseases are frequent, and their prevalence and severity differ in the different regions of the world. Any animal, whether mammal, reptile, or insect can cause allergy in a sensitized person. In this report, we describe an unusual case of exclusive allergic sensitization to Korean squirrel (*Eutamias sibiricus*), commonly called chipmunk, which belongs to the genus *Tamias* from the family Sciuridae; there are approximately 25 species under this name, mainly in North America, although it is a species native to Asia. The Korean squirrels belong to this group; in comparison with other rodents, Korean squirrels have a sharp head and small ears. Adults are between 14–19 cm long, and they weight between 100–125 g. Its color can range from light brown to reddish, and its hair is soft and short. The name chipmunk comes from the several lists that cover its body. They are usually quiet and live in a cage, so it is easier to clean them; taking care of them is not difficult and does not require a lot of time.

We present the case of a 47-year-old woman diagnosed as having latex allergy with no other known illnesses. She was referred to our allergy clinic because she presented with persistent rhinoconjunctivitis and daily asthmalike symptoms, shortness of breath, and wheezes, identified by her physician. During the last year she had had a Korean squirrel in her house.

The results of a skin prick test with common inhalant allergens were positive for *Cupressus* and grass pollen and negative for animal dander (rabbit, horse, rat, cat, dog, mouse, and hamster). Prick by prick skin test with Korean squirrel dander was performed, being positive with a wheal of 8 mm in diameter.

Spirometry revealed normal values (forced vital capacity [FVC], 2.86 L; forced expiratory flow in 1 second [FEV₁], 2.39 L; FEV₁/FVC ratio, 83%), a negative bronchodilator test result, and a fraction of exhaled nitric oxide of 73 ppb.

A methacholine test result at baseline was negative (provocation concentration that caused a decrease in FEV₁ of 20%, >16 mg/mL). Specific bronchial challenge with Korean chipmunk dander extract was performed, and she had an immediate asthmatic reaction with a maximal decrease in FEV₁ of 18.5%, dyspnea, and oral pruritus; no late asthmatic reaction was observed. Bronchial challenge with methacholine was assessed 24 hours after the specific challenge, with negative results (provocation concentration that caused a decrease in FEV₁ of 20%, >16 mg/mL). No changes in fraction of exhaled nitric oxide were observed.

Korean chipmunk dander extract was made and used at a concentration of 2.87 mg/mL for in vitro tests. Sodium dodecylsulfate–polyacrylamide gel electrophoresis was performed with this extract under reducing conditions. One prominent protein band at 15 kDa was observed. Immunoblots were also performed with the extract and patient serum (one-third dilution), obtaining a specific immunoglobulin E (IgE)-binding band at the same molecular weight of 15 kDa (Fig 1).

Mass spectrometry was performed by digestion with trypsin to identify this protein. De novo sequencing was performed, and 2 peptides were obtained (YMEGVDR and HIVMDGDGLAVNVVTPFR),

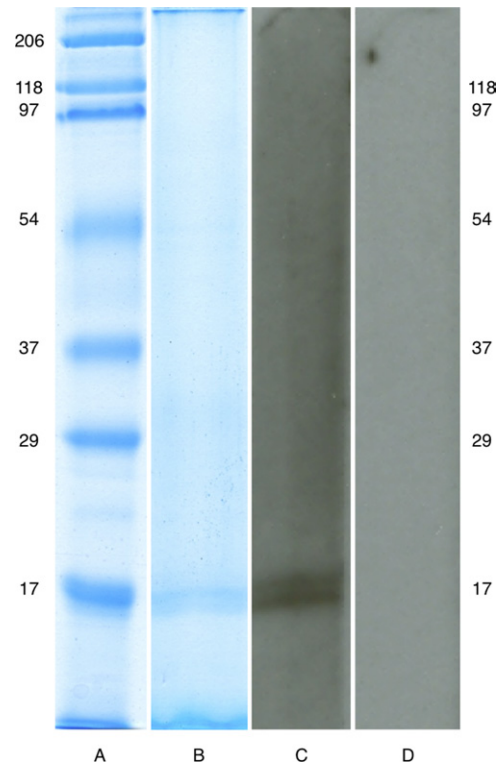


Fig 1. Sodium dodecylsulfate–polyacrylamide gel electrophoresis with Korean squirrel extract (A: molecular weights, B: Korean squirrel extract, 40 μ g) and IgE immunoblot with Korean squirrel extract (C: patient serum, D: negative control serum).

which did not present significant homology with known proteins after searching in a nonredundant protein sequence database (National Center for Biotechnology Information). This protein could be a new allergic protein that has not been identified in pets yet.

The patient was advised to remove the chipmunk from the house, and she has had no symptoms since she gave the chipmunk away.

The animals currently considered as pets are substantially different from the fish, cats, and dogs that were so usual 20 years ago. People look for much more exotic creatures as pets, and rodents in particular are becoming popular not only among children but also adults. Hamsters were the first rodents that became popular and also became a new cause of asthma,^{1,2} but recently many more cases of allergy to several other kinds of pets have been described.^{3,4}

We present the first case report, to our knowledge, of asthma due to Korean chipmunk hair in which an IgE mechanism has been demonstrated. The protein responsible for this allergy could be a new allergen different from the lipocalin family proteins.

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