



Rabbit allergens: A significant risk for allergic sensitization in subjects without occupational exposure

G. Liccardi^a, A. Piccolo^a, B. Dente^b, A. Salzillo^a, P. Noschese^a,
J.A. Gilder^c, M. Russo^a, G. D'Amato^{a,*}

^aDepartment of Chest Diseases, Division of Pneumology and Allergology, High Speciality "A.Cardarelli" Hospital, Via Rione Sirignano no 10, 80122 Naples, Italy

^bLaboratory of Clinical Pathology, "San Paolo" Hospital, Naples, Italy

^cScientific Communications, Naples, Italy

Received 23 June 2005; accepted 12 November 2005

KEYWORDS

Bronchial asthma;
Pets;
Rabbit;
Respiratory allergy;
Rhinitis

Summary

Background: Although rabbits are becoming popular as pets, data about the characteristics of allergic sensitization to rabbit allergens in patients without professional exposure are scarce.

Aims of the study: To determine the characteristics of allergic sensitization to pet rabbits, and the role of direct and indirect exposure to rabbits and rabbit allergens in non-professionally exposed patients.

Methods: From among 1124 consecutive outpatients, we selected all subjects with an immediate skin reaction to rabbit dander. A *clinical history* including a careful evaluation of the modality of rabbit exposure, the results of skin-prick tests (SPTs) and total/specific IgE antibodies were recorded. The prevalence of rabbit ownership in the Naples area was also calculated.

Results: Among 753 SPT-positive patients, 20 (2.65%) were sensitized to rabbit dander (5 patients were mono-sensitized). Fifteen patients reported direct rabbit contact (7 were rabbit owners and 8 had occasional contact outside the home); 3 patients had indirect exposure through contact with rabbit owners and 2 patients denied any direct or indirect exposure. Rabbit mono-sensitized owners of pet rabbits had persistent (moderate-severe) symptoms. The prevalence of rabbit ownership is 1.56%.

Conclusions: In susceptible not professionally exposed individuals, direct rabbit contact and, in some cases, indirect or no apparent exposure, may induce allergic sensitization to rabbit allergens. A progressive increase in rabbit sensitization (also

*Corresponding author. Tel.: +39 081 7473335 4 3; fax: +39 081 7473331.
E-mail address: gdamato@qubisoft.it (G. D'Amato).

by indirect exposure) may be expected as a consequence of the increase in rabbit ownership.

© 2006 Elsevier Ltd. All rights reserved.

Introduction

Exposure to rabbit allergens is a frequent occupational hazard for people who are in regular contact with these animals in the laboratory and in other professional settings.^{1,2} Although rabbits (*Oryctolagus cuniculus*) are becoming popular as pets in Italy and elsewhere, there are very few reports of allergic sensitization to rabbit-derived allergens because of domestic exposure.³⁻⁵

We recently reported a case of severe respiratory allergy induced by indirect exposure to rabbit allergens through the clothes of a rabbit owner.⁶ This modality of allergic sensitization is very frequent in patients sensitized to cat and dog allergens who do not have animals at home.⁷⁻⁹ Differently, no study has evaluated the role of direct or indirect exposure to rabbit allergens in developing allergic sensitization to these allergens. The aim of this report was to investigate the characteristics of allergic sensitization to rabbit allergens in patients without professional exposure, and the potential modality of exposure.

Methods

Patients

We examined 1124 subjects ranging in age between 2 and 76 years (mean age 28.8; 544 males and 580 females) living in the Naples area. Of these subjects who were consecutively evaluated in our Allergy Service from 1 October 2003 to 31 October 2004 for respiratory symptoms of a suspected IgE-mediated aetiology, we selected all patients showing an immediate skin reaction to rabbit dander. An internal *case report form (CRF)* specifically de-

signed for this study was completed by the allergists during the screening consultation in all patients. Our CRF contained all informations about each patient such as: age, family history of allergy, characteristics of domestic environment, previous and current anamnestic data, type and age of onset of clinical symptoms, periods of symptoms and possible exposure to a rabbit, cat or dog, the results of skin-prick test (SPT) and previous/current pharmacological treatments. Since the absence of a pet at home does not exclude direct exposure to a pet outside the home,¹⁰ we classified cat, dog and rabbit contact in our rabbit-sensitized patients into four categories (Table 1). Nasal and bronchial symptoms were classified according to international guidelines.^{11,12}

Allergen extracts and skin-prick tests

The commercial allergen extracts used for screening SPTs were provided by ALK Abello Group, Milan Italy. The routine panel of allergens was constituted by *Dermatophagoides pteronyssinus*, *D. farinae*, *Alternaria alternata*, *Cladosporium herbarum*, pet hair (cat, dog and rabbit), *Parietaria*, grass mix, *Artemisia vulgaris*, *Olea europaea*, *Betula pendula*, *Cupressus sempervirens* and *Corylus avellana*. These allergens were considered the most frequent causative agents of respiratory allergy in our geographical area. Positive (10 mg/ml histamine HCl) and negative (saline solution in glycerine-phenol solution) controls were used to verify a normal cutaneous response.

SPTs were carried out and interpreted according to international guidelines¹³: the result was read after 15 min and expressed as the major diameter of the wheal and its orthogonal. A skin reaction of 3 mm or greater was considered positive.

Table 1 Classification of pet exposure in rabbit-sensitized patients.

Animal at home: Patients with pets in the home for at least 2 years

Occasional contact: Patients without pets at home but on some occasions in close contact with pets outside the home

Indirect exposure: Patients who denied any direct exposure with pets but who can be indirectly exposed to pet allergens through contact with pet owners

*No contact**: Patients who denied any apparent direct or indirect exposure to rabbit /rabbit allergens

*Not applicable to cat and dog because of the well-known "ubiquity" of their allergens.

Serum collection and evaluation of total and specific IgE antibodies

Approximately 4 ml of serum was collected from each rabbit-dander sensitized patient and stored at -20°C .

Total and specific IgE for rabbit allergens (dander, urine, serum and meat), and all allergens that induced SPT positivity were determined by the Pharmacia CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden).

Statistical analysis

Statistical significance was evaluated by using the paired *t*-test, mean values, and 95% confidence interval of the differences on data normalized by log conversion.

Prevalence of rabbit ownership in the Naples area

The prevalence of rabbit ownership in the families of Naples area was calculated by telephone interviews on a random sample of 1601 families by simply asking whether they had or not a rabbit at home. The area in which the prevalence of rabbit ownership was calculated coincided with the area where the enrolled patients live.

Results

A total of 753 patients had positive SPT for at least one allergen; 371 individuals were not sensitized. Of the 753 sensitized subjects, 20 (2.65%) were sensitized to rabbit dander. The main demographic data and rabbit-related diagnostic results of the latter subjects are listed in Table 2. Five subjects were sensitized exclusively to rabbit allergens, whereas 15 were sensitized also to other common allergens. Fifteen subjects reported direct rabbit contact (seven for rabbit ownership and eight for occasional contact outside the home), three subjects excluded any direct exposure to the animal but had occasional contact with rabbit owners, and finally two subjects denied any apparent direct or indirect exposure to rabbit or rabbit allergens.

Eighteen of the 20 rabbit-sensitized patients reported both nasal and bronchial symptoms, one reported rhinitis without asthma and one asthma without rhinitis. All five non-smoking rabbit mono-sensitized patients had associated nasal and bronchial symptoms. One individual reported both intermittent nasal and bronchial symptoms, four patients persistent nasal (three moderate-severe

and one mild) and bronchial (two moderate and two severe) symptoms. In the three rabbit mono-sensitized patients who had a rabbit at home, the latent interval from first contact with this animal to the development of respiratory symptoms ranged between 3 and 5 months. Since 15 rabbit-sensitized patients had cutaneous and serological responses to such other allergens as those derived from mites, pollens and cat/dog, we cannot quantify the role of rabbit sensitization on patients' symptoms. However, it is important to outline that in polysensitized subjects, the role of allergic sensitization to common pets such as cats and dogs in inducing clinical symptoms may be difficult to establish. Individuals with a rabbit at home and those with occasional direct contact had more intense cutaneous and serological responses to rabbit allergens than did indirectly or apparently not exposed patients. However, as indicated in Table 3, there are no significant differences between the results of SPTs and specific IgE determinations in patients with animal at home (Aah) and those with occasional rabbit contact (Oc). With the exception of specific IgE antibodies against Re 211 (rabbit urine), there are no significant differences between the results of SPTs and specific IgE in patients with Oc/Aah and those never in contact (Nc) with rabbits. This finding is not surprising because only people with rabbit at home may be exposed and, consequently, sensitized to the urine of this animal.

Apart from one patient, all subjects without direct contact with a rabbit had negative serological responses to rabbit urine and serum. We found specific IgE antibodies against rabbit meat only in three out of 20 SPT-rabbit-positive patients. None of these patients reported any adverse reaction after the ingestion of rabbit meat.

The prevalence of rabbit ownership in the Naples area is 1.56%. As monoclonal antibody-based methods to measure the amount of rabbit allergen in the dust of indoor environments are not available, we have no information on the levels of exposure to this allergen.

Discussion

The results of our study suggest that, in susceptible individuals, rabbit contact (rabbit ownership or occasional contact) is a risk factor for the development of allergic sensitization to rabbit allergens. However, some indirectly or apparently not exposed individuals showed a moderate or low degree of sensitization to rabbit allergens. The observation that indirect exposure to rabbit allergens might be

Table 2 Demographic data and diagnostic results in rabbit-sensitized patients.

Sex (M/F)	Age (y)	Family history of allergy	Contact with pets			Clinical symptoms	Diagnostic results			
			Dog	Cat	Rabbit		Skin-prick tests		Specific IgE	
							Rabbit dander (Rd) (Wheal diameter)	Other allergens	Allergen	Ku/L/Class
F	18	No	le	Oc	Oc	R+C+A	7 × 4 mm	DP,DF,D, C,P,Gr, Av,Ol	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 1.3/2 <0.35/0
F	36	No	le	le	le	R+C	8 × 5 mm	D,Ol	Re 206 Re 211 e 82 f 213	<0.35/0 3.5/3 7.5/3 <0.35/0
M	23	Yes	Aah	Oc	Oc	R+C	5 × 5 mm	Av	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 <0.35/0 <0.35/0
M	33	Yes	le	le	Oc	R+A	6 × 5 mm	P,Av,C	Re 206 Re 211 e 82 f 213	<0.35/0 2.0/2 2.4/2 0.35/0
F	35	No	le	le	Aah	R+A	8 × 5 mm	DP,DF,P	Re 206 Re 211 e 82 f 213	78.3/5 88.2/5 >100/6 9.0/3
M	16	Yes	le	le	le	R+C	4 × 4 mm	DP,DF,P,D,C,Gr, Av,Ol	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 0.65/1 0.35/0
F	62	Yes	Aah	le	le	A	4 × 4 mm	DP,DF,P,Gr,D,C	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 <0.35/0 <0.35/0
M	40	Yes	le	le	Oc	R+A	8 × 6 mm monosensitized	n.a.	Re 206 Re 211 e 82 f 213	7.6/3 24.3/4 34.2/4 3.7/3
F	46	Yes	le	Aah	Oc	R+A	6 × 4 mm	P,Av,Ol	Re 206 Re 211 e 82 f 213	<0.35/0 5.3/3 8.2/3 <0.35/0
F	13	No	le	le	Aah	R	4 × 4 mm	DP,Df,C	Re 206 Re 211 e 82 f 213	<0.35/0 1.1/2 !3/2 0.7/1
M	30	Yes	Oc	Oc	Oc	R+A	4 × 5 mm	P,D,C	Re 206 Re 211 e 82 f 213	2.6/2 1.0/2 0.6/1 0.4/1
M	42	Yes	le	le	Aah	R+A	6 × 6 mm	DP,DF,D,C,Al	Re 206 Re 211 e 82 f 213	<0.35/0 7.2/3 9.8/3 <0.35/0

Table 2 (continued)

Sex (M/F)	Age (y)	Family history of allergy	Contact with pets			Clinical symptoms	Diagnostic results				
			Dog	Cat	Rabbit		Skin-prick tests		Specific IgE		
							Rabbit dander (Rd) (Wheal diameter)	Other allergens	Allergen	Ku/L/Class	
F	38	Yes	le	le	Oc	R+A	5 × 4 mm monosensitized	n.a.	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 <0.35/0 <0.35/0	
F	33	Yes	le	le	Nc	R+C+A	5 × 5 mm	DP,DF,P,Gr,D,C	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 1.4/2 <0.35/0	
F	14	Yes	le	le	Oc	R+C+A	6 × 6 mm	P,Gr,Av	Re 206 Re 211 e 82 f 213	<0.35/0 1.0/2 1.2/2 <0.35/0	
F	20	No	le	le	Nc	R+C+A	5 × 5 mm	DP,DF,D,Ol	Re 206 Re 211 e 82 f 213	<0.35/0 <0.35/0 <0.35/0 <0.35/0	
F	10	No	le	le	Aah	R+A	9 × 7 mm monosensitized	n.a.	Re 206 Re 211 e 82 f 213	0.8/2 6.3/3 18.4/4 <0.35/0	
F	15	No	le	le	Aah	R+A	10 × 11 mm monosensitized	n.a.	Re 206 Re 211 e 82 f 213	1.1/2 1.7/2 301.4/6 <0.35/0	
F	20	Yes	lc	Aah	Aah	R+C	6 × 5 mm	DP,DF,P,Gr	Re 206 Re 211 e 82 f 213	0.8/2 0.6/1 0.9/2 <0.35/0	
M	49	No	lc	lc	Aah	R+A	8 × 6 mm monosensitized	n.a.	Re 206 Re 211 e 82 f 213	0.4/1 4.9/3 8.1/3 <0.35/0	

Aah, animal at home; Rd, rabbit dander; DP, Dermatoph.pter; le, indirect exposure; Re 206, rabbit serum; DF, Dermatoph.far.; Oc, occasional contact; Re 211, rabbit urine; P, Parietaria; Nc, no contact; e 82, rabbit dander; Gr, Grasses; R, rhinitis; f 213, rabbit meat; Av, Artemisia vulgaris; C, conjunctivitis; Ol, Olea europaea; A, bronchial asthma; D, Dog dander; n.a., not applicable; C, Cat dander; Al, Alternaria.

responsible for allergic sensitization confirmed our earlier report on this topic.⁶

It is not easy to explain allergic sensitization to rabbit allergens in the two patients (one of whom showed also serological sensitization to rabbit dander) who denied exposure to rabbit and rabbit allergens. A possible reason could be cross-reactivity between rabbit allergens (recently identified as members of the lipocalin super-family),¹⁴ and

lipocalins of such other animal species as horse, cow, dog, guinea pig, mouse, and cat.¹⁵⁻²⁰

Respiratory symptoms were persistent and moderate-severe in the three rabbit-mono-sensitized individuals with rabbit at home of our study. This finding is in agreement to Yarnell et al.²¹ who studied 2484 children from 26 schools in Northern Ireland using questionnaires (core ISAAC questions). They found that the ownership of some small furry

Table 3 Results of statistical analysis.

Rabbit contact	Skin-prick tests Rabbit dander Wheal diameter (mm)	Specific IgE		
		Rabbit Re 206 (Ku/L)	Rabbit Re 211 (Ku/L)	Rabbit e 82 (Ku/L)
Oc				
M	3.32	-0.41	0.30	0.54
SD	0.30	1.21	1.51	1.60
Aah				
M	3.74	0.14	1.43	2.54
SD	0.60	1.92	1.64	2.12
	$t = 1.752$	$t = 0.673$	$t = 1.389$	$t = 2.080$
	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Oc+Aah				
M	3.52	-0.15	0.83	0.47
SD	0.50	1.55	1.63	2.06
NC				
M	3.13	-1.05	-1.05	-0.04
SD	0.38	0	0	1.28
	$T = 1.562$	$t = 1.272$	$t = 2.537$	$t = 1.524$
	$P > 0.05$	$P > 0.05$	$P < 0.05$	$P > 0.05$

animals (rabbits, guinea pigs or gerbils) as a household pet was independently associated with both severe wheeze and asthma or treated wheeze. No such association was observed with the ownership of other pets (cat and dog).

In conclusion, rabbit allergens represent an often underestimated cause of allergic sensitization, and in some cases, of clinical symptoms in susceptible individuals also in the absence of professional exposure. Although rabbit contact represents a higher risk factor, also occasional direct and, less frequently, indirect exposure may induce allergic sensitization. The prevalent modality of direct exposure for inducing sensitization is probably due to the rather low rate of rabbit ownership (1.56%) in our geographical area as compared with cat/dog ownership. On the contrary, a large proportion of patients sensitized to cat and/or dog allergens are only indirectly exposed to these pets. A progressive increase in rabbit sensitization (also by indirect exposure) may be expected in the future as a consequence of the increase in rabbits as pets. At least in Italy some indirect indexes suggest an increasing trend of rabbit ownership, in fact commercial sources indicate an increasing business in rabbit breeding as well as in production of rabbit-related materials (food, accessories etc). Finally, we suggest that SPTs and/or radio-allergo-sorbent tests for rabbit allergens be performed in all potentially susceptible individuals before the introduction of a rabbit indoors also in the absence

of respiratory symptoms after previous occasional rabbit contact.

References

- Bush RK, Wood RA, Eggleston PA. Laboratory animal allergy. *J Allergy Clin Immunol* 1998;**102**:99-111.
- Ruoppi P, Koistinen T, Susitaival P, Honkanen J, Soininen H. Frequency of allergic rhinitis to laboratory animals in university employees as confirmed by chamber challenges. *Allergy* 2004;**59**:295-301.
- Hommura F, Munakata M, Doi I, Nasuhara Y, Kawakami Y. Pulmonary infiltration with eosinophilia due to rabbit-fur antigen: diagnosis by allergen inhalation test. *Japan J Thor Dis* 1997;**35**:455-60.
- Prince E, Zacharisen MC, Kurup VP. Anaphylaxis to rabbit: a case report. *Ann Allergy Asthma Immunol* 1998;**81**:272-3.
- Lelong M, Bras C, Thelliez P, Drain JP. Does the allergic child become sensitized to small domestic mammals (guinea pig, hamster, rabbit?). *Allerg Immunol (Paris)* 1990;**22**: 23-5.
- Liccardi G, D'Amato G, Canonica GW, Dente B, Passalacqua G. Severe respiratory allergy induced by indirect exposure to rabbit dander: a case report. *Allergy* 2004;**59**: 1237-8.
- D'Amato G, Liccardi G, Russo M, Barber D, D'Amato M, Carreira J. Clothing is a carrier of cat allergens. *J Allergy Clin Immunol* 1997;**99**:577-8.
- Custovic A, Taggart S, Woodcock A. House dust mite and cat allergen in different indoor environments. *Clin Exp Allergy* 1994;**24**:1164-8.
- De Lucca SD, O'Meara TJ, Tovey ER. Exposure to mite and cat allergens on a range of clothing items at home and the transfer of cat allergen in the workplace. *J Allergy Clin Immunol* 2000;**106**:874-9.

10. Almqvist C, van Hage-Hamsten M. Cat and dog allergens—can intervention studies solve their inscrutable riddle? *Clin Exp Allergy* 2003;**33**:1167–70.
11. Bousquet J, The ARIA Workshop Group. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147–336.
12. Global Initiative for Asthma. <http://ginasthma.com>.
13. Dreborg S, Frew A., editors. Position paper: allergen standardization and skin tests. *Allergy* 1993;**48**(Suppl 14): 49–82.
14. Baker J, Berry A, Boscato LM, Gordon S, Walsh BJ, Stuart MC. Identification of some rabbit allergens as lipocalins. *Clin Exp Allergy* 2001;**31**:303–12.
15. Gregoire C, Rosinski-Chupin I, Rabillon J, Alzari PM, David B, Dandeu JP. cDNA cloning and sequencing reveal the major horse allergen *Equ c 1* to be a glycoprotein member of the lipocalin superfamily. *J Biol Chem* 1996;**271**:32951–9.
16. Mantyjarvi R, Parkkinen S, Ryttonen M, Pentikainen J, Pelkonen J, Rautiainen J, et al. Complementary DNA cloning of the predominant allergen of bovine dander: a new member in the lipocalin family. *J Allergy Clin Immunol* 1996;**97**:1297–303.
17. Konieczny A, Morgenstern JP, Bizinkauskas CB, Lilley CH, Brauer AW, Bond JF, et al. The major dog allergens, *Can f 1* and *Can f 2*, are salivary lipocalin proteins: cloning and immunological characterization of the recombinant forms. *Immunology* 1997;**92**:577–86.
18. Fahlbush B, Rudeschko O, Szilagyi U, Schlott B, Henzgen M, Schlenvoigt G, et al. Purification and partial characterization of the major allergen *Cav p 1*, from guinea pig *Cavia porcellus*. *Allergy* 2002;**57**:417–22.
19. Clark AJ, Ghazal P, Bingham RW, Barrett D, Bishop JO. Sequence structures of a mouse major urinary protein gene and pseudogene compared. *Embo J* 1985;**4**:3159–65.
20. Smith W, Butler AJL, Hazell LA, Chapman MD, Pomes A, Nickels DG, et al. *Fel d 4,a* cat lipocalin allergen. *Clin Exp Allergy* 2004;**34**:1732–8.
21. Yarnell JWG, Stevenson MR, MacMahon J, Shields M, McCrum EE, Patterson CC, et al. Smoking, atopy and certain furry pets are major determinants of respiratory symptoms in children: the International Study of Asthma and Allergies in Childhood Study (Ireland). *Clin Exp Allergy* 2003;**33**: 96–100.