

G. LICCARDI¹, A. SALZILLO¹, M. SOFIA², A. PICCOLO¹, B. DENTE³, M. RUSSO¹,
M. D'AMATO², A. STANZIOLA², G. D'AMATO¹

Sensitization to rodents (mouse/rat) in an urban atopic population without occupational exposure living in Naples, Italy

¹Department of Chest Diseases, Division of Pneumology and Allergology. High Speciality "A. Cardarelli" Hospital, Naples, Italy - E-mail: gennaro.liccardi@tin.it

²Division of Respiratory Medicine. High Speciality "V. Monaldi" Hospital and University "Federico II", Naples, Italy

³Laboratory of Clinical Pathology, "San Paolo" Hospital, Naples, Italy

KEY WORDS

Allergic rhinitis, bronchial asthma, mouse, rat, pet allergy

Corresponding author

Gennaro Liccardi, MD
Department of Chest Diseases,
Division of Pneumology and
Allergology
High Speciality "A. Cardarelli"
Hospital. Piazzetta Arenella n° 7 -
80128, Naples, Italy
Phone: +390817473335-4-3;
Fax: + 39 081 7473331;
E-mail: gennaro.liccardi@tin.it

SUMMARY

Background: Until now no data on allergic sensitization to rodents allergens in Western Europe and Italy are available. The aim of this report was to investigate clinical significance and characteristics of IgE-mediated sensitization to mouse/rat (M/Rt) allergens in atopic subjects not occupationally exposed to these animals and living in urban area of Naples. **Methods:** In 1765 consecutive outpatients, we selected all subjects with an immediate skin reaction to M/Rt dander. Clinical history including a careful evaluation of the modality of exposure, the results of skin-prick tests (SPTs) and specific IgE antibodies were recorded. **Results:** Among 1185 SPT-positive patients, 22 were sensitized to M/Rt dander (respectively 1.60% and 0.59%). No patient was mono-sensitized. Only three of 22 patients reported indoor conditions suggesting presence of rodents allergens at home. All patients exhibited low degree of SPT positivity and low levels of circulating IgE antibodies to M/Rt. High frequency of concomitant allergic sensitization to pet (and other animal) dander has been found. **Conclusions:** Our results suggest that role of allergic sensitization to rodents is negligible in atopic subjects without occupational exposure living in urban area of Naples. However, highly atopic individuals especially those already sensitized to common pet dander should be tested by SPTs/evaluation of serum specific IgE to rodents in the case they could begin an occupational exposure to M/Rt or keeping these animals as pets.

Introduction

Rodents (mouse and rats - M and Rt) constitute a well recognized cause of allergic sensitization and bronchial asthma in several occupationally exposed individuals such as research scientists, technicians and animal handlers (1). More recently, it has been shown that M and Rt allergens play a significant role as sensitizing agents of airways in domestic environments especially in some geographic areas such as United

States (2-7). At the best of our knowledge only two studies on clinical aspects of rodent allergy have been published in Poland and Turkey (8,9), while no data are available in other parts of the world including Western Europe and Italy.

The objective of our prospective study was to assess the prevalence of allergic sensitization, clinical characteristics and modality of exposure to common rodents (M/Rt) in a sample of atopic population without occupational exposure living in Naples area, Italy.

Methods

1765 subjects aged between 7 and 76 years (mean age 33.2) living in Naples area and consecutively evaluated in our Allergy Service from 1 January 2008 to 31 December 2009 for respiratory symptoms of a suspected IgE-mediated aetiology were examined.

A case report form (CRF) containing all information and specifically designed for this study was completed during the screening consultation of each patient. The standardized form reported: demographic data, type and duration of respiratory symptoms, pets ownership, possible exposure to rodent allergens as assessed by some predictors (such as evidence of M/Rt/cockroach presence, poor housing conditions etc), results of the skin prick tests (SPTs), results of specific IgE evaluation for M/Rt dander. The forms were filled by the allergist, who also verified the consistency of clinical history and SPT results and the same doctor confirmed the diagnosis of respiratory allergy according to the International Guidelines (10,11). Subjects with occupational exposure to rodents (workers exposed to laboratory animals in the pharmaceutical industry, university laboratories, research units, rodent breeding facilities or veterinary doctors) were not considered. We excluded also individuals working at mouse facilities including those non-mouse handling (12). To avoid the passive transport of rodents allergens at home, patients living together families occupationally exposed to M/Rt were excluded (13). Patients with chronic infectious diseases, malignancies or dysmetabolic diseases, severe cutaneous disorders, negative skin reaction to histamine, or in treatment with drugs interfering with the skin response were excluded as well.

Since the absence of a pet at home does not exclude a direct exposure to pet outside and considering the peculiarity of possible contacts with rodents, we classified animal exposure into two categories:

- Positive contact: about pets, the presence of these animals at home or frequent direct contacts for different reasons (e.g. hobby, sport etc), as regard rodents predictors for presence of allergens in indoor environments.
- Negative contact: regarding pets any direct pet contact but an indirect exposure though the contact with pet owners/any apparent direct or indirect exposure. Regarding rodents any apparent predictors for presence of allergens in indoor environments.

The commercial allergen extracts used for screening SPTs were provided by Lofarma Laboratories, Milan, Italy. We used a standard panel of allergens including: *Der-*

matophagoides pteronyssinus and *D. farinae*, *Alternaria alternata*, *Cladosporium herbarum*, cat, dog, *Parietaria*, Grass mix, *Artemisia vulgaris*, *Olea europaea*, *Betula pendula*, *Cupressus sempervirens* and *Corylus avellana*. These allergens cover the majority of causative agents of respiratory allergy in Italy. In addition we used allergenic extracts of rodents (M and Rt) and other furry animals (horse, rabbit, guinea pig, hamster, cow hair).

Positive (10 mg/ml histamine HCl) and negative (saline solution in glycerine-phenol solution) controls were used as well. SPTs were carried out and interpreted according to international guidelines (14). The result was read after 15 minutes and expressed as the mean of the major wheal diameter plus its orthogonal. A skin reaction of 3 mm or greater was considered positive.

The profile of the wheals were outlined using a fine-point marking pen and transferred by adhesive tape onto patient's form.

Approximately 4 ml of serum was collected from each M/Rt dander – sensitized patients and stored at -20°C. Specific IgE for M (e71) and Rt (e73) dander were determined by the CAP System FEIA (Thermofisher Scientific-Immuno-Diagnostics, Milan, Italy).

Results

A total of 1765 patients were examined. In this context 1185 (67.13%) had a SPTs positivity for at least one allergen and were diagnosed as having respiratory allergy. The 1185 SPT-positive subjects had a mean age of 33.2 years (range 8-73) and 655 (55.27%) of them were female. Twenty two were sensitized to rodents (15 patients only to M, 3 only to Rt and 4 to both M and Rt allergens), 16 patients were females and only 6 males. Thus, the overall sensitization prevalence in subjects with respiratory allergy was 1.60% for M and 0.59% for Rt. No patient was mono-sensitized to rodents. Eighth patients reported rhinitis (R) + bronchial asthma (A), 5 R+A+ conjunctivitis (C), 5 R+C, 3 only A and 1 individual only R. Thirteen patients exhibited persistent and 9 intermittent symptoms. Only 3 out of 22 patients reported some indoor conditions which constitute predictors for the presence of rodents allergens. In 2 of these individuals (PF and MM) we found the higher levels of cutaneous and serological sensitization to M/Rt, the remaining patients exhibited low degree of SPT positivity and low levels of circulating IgE for M/Rt (in 16 out of 22 individuals evaluation of M/Rt specific IgE antibodies was negative).

Since all M/Rt sensitized patients showed cutaneous positivity to other common allergens (mites, pollens, moulds and pets) we could not quantify the role of rodents sensitization in eliciting symptoms. The most common sensitizing allergens associated M/Rt allergic individuals are reported in Figure 1. Cat dander constitutes the first cause of associated sensitization followed by *Parietaria*, dog dander, mites and grasses. An interesting observation is the high percentage of allergic sensitization to pet (and other animal) dander in individuals with M and Rt allergy. In our geographical area, sensitization to pets is significantly lower in comparison to that induced by *Parietaria*, mites and grasses (15,16).

Because monoclonal antibody-based methods to measure the amount of M/Rt allergens in the dust of indoor environments are not available in Italy, we have not information about the levels of indoor exposure to these allergens. However, Curtis-Brosnan et al. (17) have shown that patient report on the presence of rodents at home and some predictors such as cockroach infestation and poor housing conditions may be sufficient to hypothesize M/Rt allergen exposure in indoor environments.

The main characteristics of the patients sensitized to M/Rt are summarized in Table 1.

Discussion

Rodent's allergens, especially those of M and in a lesser extent of Rt, constitute a common cause of allergic sensitization and bronchial asthma in children and adult populations of US living in inner cities (2,5). It has been shown

that current asthma, defined as having doctor-diagnosed asthma and asthma symptoms in the preceding 12 months, was positively associated to increasing levels of M allergens at home (3). Furthermore, the sensitized and exposed children were at higher risk for hospitalization for asthma (18). This high rate of allergic sensitization to rodents reflect the high levels of M/Rt allergens in inner-city US homes and schools (5,19-21). In fact, some environmental conditions such as low-income housing, building-level and neighbourhood-level characteristics are associated to rodents as well as other pest infestations (22,23).

The results of our study suggest that the prevalence of allergic sensitization to M and Rt allergens is low in urban atopic population living in Naples area. The main characteristics of M/Rt sensitized individuals (prevalence of female sex, high rate of family history of allergy, periods and type of clinical symptoms) may be easily explained by associated sensitizations to other common allergens involved in all individuals. Our data confirm the reported outstanding role of SPT on specific IgE evaluation in discriminating patients sensitized to M allergens (24,25), in fact only 6 out of 22 patients had circulating M/Rt specific IgE antibodies. However, no specific symptoms related to exposure to rodents were found in patients with higher degree of cutaneous/serological sensitization to M/Rt. The low prevalence of allergic sensitization to M/Rt allergens in our study is probably due to the rare reported presence (only in three cases) of environmental conditions commonly considered at high risk for rodent allergens presence (17). As a consequence, we cannot exclude that a survey carried out specifically in low-income districts of Naples area could exhibit higher prevalence of sensitization.

An important finding of our study was the high prevalence of allergic sensitization to animal dander in M/Rt sensitized individuals with or without pet contact. In this group of patients cat dander is the most common sensitizing agent, our previous reports have shown that mites, parietaria, grasses and olea constitute the most common causes of respiratory allergy in Naples area (15,16). This finding confirms our recent report that allergic sensitization to furry animals (cat, dog, horse, guinea pig, rabbit, hamster, cow etc.) may be induced in susceptible individuals with or without animal exposure (26-28) A possible explanation for high prevalence of mammals sensitization in subjects without known contact with animals could be an indirect exposure or a cross-allergic reaction induced by lipocalins (29) and serum albumin (30). Furthermore, we have recently suggested a possible predisposition (allergic phenotype?) to develop multiple sensitization to

Figure 1 - Associated sensitizations.

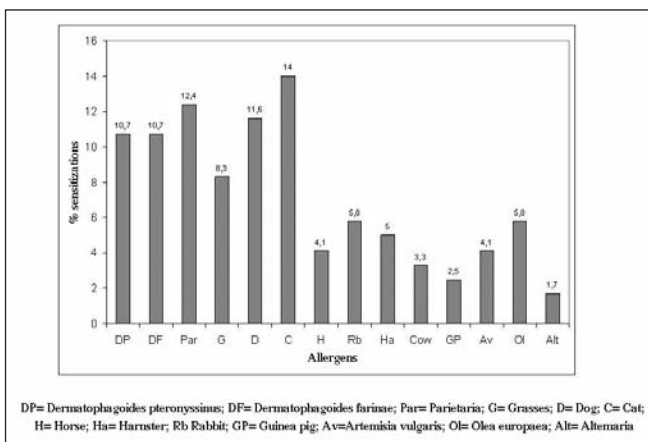


Table 1 - Characteristics of patients sensitized to mouse/rat allergens.

Demographic Data				Clinical Data				Diagnostic Results			
ID	Sex (F/M)	Age (Y)	Family history of allergy	Predictors for rodents' allergen presence	Pet Contact	Clinical Symptoms	Periods	Skin-prick tests		Specific IgE	
								Mouse/Rat dander (Wheal diameters)	Other allergens	Allergen	Kda/Class
CM	M	16	YES	NO	YES	RC	I	Rt (4X4) M(4X3)	Par, G, D, Cat, H, R, Ha, Cow, GP	e 71 e 73	<0.350 <0.350
DVA	M	26	YES	NO	YES	RC	I	Rt (8X7)	DP, DF, Par, Cat, Ha	e 73	0.7/1
DDM	F	28	YES	NO	YES	R	P	M (4X4)	Par, G, Av, Ol, D, Cow,	e 71	<0.350
FS	F	26	YES	NO	YES	RA	P	M (3X4)	DP, DF, Par, D, Cat, Av	e 71	<0.350
FF	F	25	YES	YES	YES	A	I	Rt (9X6)	DP, DF, Ol, H, R, Ha	e 73	1.2/1
MM	F	27	NO	YES	YES	A	I	Rt (7X4) M(6X4)	DP, DF, D, Cat, R, Ha, GP	e 71 e 73	0.9/1 1.4/2
MP	M	27	NO	NO	NO	A	I	M (3X3)	DP, DF, Par, G, D, Cat, Av, Ol	e 71	<0.350
PA	F	21	NO	NO	NO	RCA	P	M (5X5)	DP, DF, Par, G, D, Cat, H, Ol, Cow	e 71	<0.350
PAn	F	64	YES	NO	YES	RC	P	M (6X4)	Par, Cat	e 71	0.6/1
LE	M	19	YES	NO	NO	RA	I	M (3X3)	Par, G, Ol, D, Cat	e 71	<0.350
HCA	F	35	YES	NO	YES	RA	P	Rt (4X4) M(6X3)	DP, DF, D, Cat, H, R	e 71 e 73	<0.350 <0.350
Rb	F	19	YES	NO	NO	RCA	I	M (4X4)	Par, G, Cat, Ha	e 71	<0.350
DMC	F	71	YES	NO	YES	RA	P	M (4X4)	DF, Par, D, Cat, H, Ol	e 71	<0.350
GA	F	61	YES	NO	YES	RA	I	M (5X4)	Par, D, Cat	e 71	0.6/1
MAM	F	39	YES	NO	YES	RA	P	M (4X3)	DP, DF, D, Cat	e 71	<0.350
CAR	F	32	YES	NO	YES	RA	P	Rt (3X4) M(3X3)	D, Cat, R, Ha, GP	e 71 e 73	<0.350 <0.350
FM	F	18	YES	NO	YES	RC	P	M (4X5)	DP, DF, Par, G, D, Cat, R, Alt	e 71	<0.350
EG	F	34	NO	NO	NO	RCA	P	M (4X3)	DP, DF, G, D, Ol	e 71	<0.350
TAV	M	18	YES	NO	NO	RC	P	M (3X4)	DP, DF, Par, G, Cat, Cow, Av, Alt	e 71	<0.350
EA	F	27	YES	NO	NO	RCA	P	M (5X5)	DP, Cat, Av	e 71	<0.350
GV	F	17	YES	NO	NO	RCA	P	Rt (4X4)	DP, DF, Par, G, R	e 73	<0.350
TR	M	70	YES	YES	NO	RA	I	M (4X4)	Par	e 71	1.1/2

DP = Dermatophagoides pteronyssinus; DF = Dermatophagoides farinae; Par = Parietaria; G = Grasses; D = Dog; Cat = Cat; H = Horse; Ha = Hamster; Rb = Rabbit; GP =Guinea pig; Av =Artemisia vulgaris; Ol = Olea europaea; Alt = Alternaria; M = Mouse; Rt = Rat. R = Rhinitis; C = Conjunctivitis; A =Bronchial asthma; I = Intermittent; P = Persistent. e 71 (M-dander); e 73 (Rt- dander)

animal allergens. In our study allergic patients sensitized to cat/dog had a fourteen time risk to develop sensitization to different furry animals in comparison to allergic patients not sensitized to common pets (31).

In conclusion, the role of allergic sensitization to rodents is negligible in atopic subjects without occupational exposure living in urban area of Naples. However, we suggest that highly atopic individuals and especially those already sensitized to common pet dander be tested by SPTs/evaluation of serum specific IgE to rodents in the case they could begin an occupational exposure to M/Rt or if they wish to keep these animals as pets. We are planning further studies examining exclusively allergic individuals living in some low-income districts of Naples area to verify a possible increase in the rate of allergic sensi-

zation to M/Rt and further testing about lipocalins or serum albumin specific IgE (to explain the sensitization in non exposed patients).

References

1. Jeal H, Jones M. Allergy to rodents: an update. Clin Exp Allergy 2010;40:1593-601
2. Matsui EC. Role of mouse allergens in allergic disease. Curr Allergy Asthma Rep 2009;9:370-75
3. Salo PM, Jaramillo R, Cohn RD, London SJ, Zeldin DC. Exposure to mouse allergen in U.S. homes associated with asthma symptoms. Environ Health Perspect 2009;117:387-91
4. Donohue KM, Al-alem U, Perzanowsky MS, et al. Anticockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. J Allergy Clin Immunol 2008; 122: 914-20

5. Matsui EC, Simons E, Rand C, et al. Airborne mouse allergen in the homes of inner-city children with asthma. *J Allergy Clin Immunol* 2005;115:358-63
6. Ahluwalia SH, Matsui EC. The indoor environment and its effects on children asthma. *Curr Opin Allergy Clin Immunol* 2011;11:137-43
7. Wang C, Abou El-Nour MH, Bennett GW. Survey of pest infestation, asthma, and allergy in low-income housing. *J Community health* 2008;33:31-39
8. Stelmach I, Jerzynska J, Stelmach W, Majak P, Chew G, Kuna P. The prevalence of mouse allergen in inner-city homes. *Pediatr Allergy Immunol* 2002;13:299-302
9. Onbasi K, Ardeniz O, Sin AZ, Kokuludaq A, Sebik F. The frequency of mouse and rat allergy among allergic individuals in Izmir (a preliminary report). *Allergy* 2004;59:1235-36
10. Bousquet J, The ARIA Workshop Group. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-S336
11. Global Initiative for Asthma. <http://ginasthma.com>
12. Curtin-Brosnan J, Paigen B, Haqberg KA, et al. Occupational mouse allergen exposure among non-mouse handlers. *J Occup Environ Hyg* 2010;7:726-34
13. Krop EJ, Doekes G, Stone MJ, Aalberse RC, van der Zee JS. Spreading of occupational allergens: laboratory animal allergens on hair-covering caps and in mattress dust of laboratory animal workers. *Occup Environ Med* 2007;64:267-72
14. Dreborg S, Frew A (Editors). Position Paper: allergen standardization and skin tests. *Allergy* 1993;48(Suppl 14):49-82
15. Liccardi G, Visone A, Russo M, Saggese M, D'Amato M, D'Amato G. Parietaria pollinosis: clinical and epidemiological aspects. *Allergy Asthma Proc* 1996;17:23-29
16. Liccardi G, Russo M, Piccolo A, et al. The perennial pattern of clinical symptoms in children monosensitized to *Olea europaea* pollen allergens in comparison with subjects with Parietaria and Gramineae pollinosis. *Allergy Asthma Proc* 1997;18:99-105
17. Curtin-Brosnan J, Matsui EC, et al. Parent report of pests and pets and indoor allergen levels in inner-city homes. *Ann Allergy Asthma Immunol* 2008;101:517-23
18. Matsui EC, Eggleston PA, Buckley TJ, et al. Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Ann Allergy Asthma Immunol* 2006;97:514-20
19. Olmedo O, Goldstein IF, Acosta L, et al. Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City. *J Allergy Clin Immunol* 2011;128:284-92
20. Sheehan WJ, Rangsithienchai PA, Muilberg ML, et al. Mouse allergens in urban elementary schools and homes of children with asthma. *Ann Allergy Asthma Immunol* 2009;102:125-30
21. Chew GL, Correa JC, Perzanowsky MS. Mouse and cockroach allergens in the dust and air in northeastern United States inner-city public high schools. *Indoor Air* 2005;15:228-34
22. Rosenfeld L, Chew GL, Rudd R, et al. Are building-level characteristics associated with indoor allergens in the household? *J Urban Health* 2011;88:14-29
23. Rosenfeld L, Rudd R, Chew GL, Emmons K, Acevedo-Garcia D. Are neighbourhood-level characteristics associated with indoor allergens in the household? *J Asthma* 2010;47:66-75
24. Sharma HP, Wood RA, Bravo AR, Matsui EC. A comparison of skin prick tests, intradermal skin tests and specific IgE in the diagnosis of mouse allergy. *J Allergy Clin Immunol* 2008;121:933-39
25. Chong LK, Ong MJ, Curtin-Brosnan J, Matsui EC. Skin test sensitivity to mouse predicts allergic symptoms to nasal challenge in urban adults. *Allergy Asthma Proc* 2010;31:472-76
26. Liccardi G, Salzillo A, Piccolo A, Russo M, D'Amato G. Sensitization to furry animals in an urban atopic population living in Naples, Italy. *Allergy* 2011; 66: 1500-01
27. Liccardi G, Passalacqua G on behalf of the Allergy Study Group of the Italian Society of Respiratory Medicine (SIMeR). Sensitization to rabbit allergens in Italy- A multicentre study in atopic subjects without occupational exposure. *Int Arch Allergy Immunol* 2006;141:295-99
28. Liccardi G, D'Amato G, Antonicelli L, et al. Sensitization to horse allergens in Italy: a multicentre study in urban atopic subjects without occupational exposure. *Int Arch Allergy Immunol* 2011; 155: 412-17.
29. Flower DR, North AC, Attwood TK. Structure and sequence relationships in the lipocalins and related proteins. *Protein Sci* 1993;2:753-61
30. Liccardi G, Asero R, D'Amato M, D'Amato G. Role of sensitization to mammalian serum albumin in allergic disease. *Curr Allergy Asthma Rep* 2011; 11: 421-26
31. Liccardi G, Passalacqua G, Salzillo A, et al. Is sensitization to furry animals an independent allergic phenotype in non occupationally exposed individuals? *J Investig Allergol Clin Immunol* 2011;21:137-41