

Role of Mouse Allergens in Allergic Disease

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Current Allergy and Asthma Reports 2009, 9:370–375

Current Medicine Group LLC ISSN 1529-7322

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Mouse allergen has long been recognized as an important cause of occupational allergy and asthma, but only recently has it been implicated in asthma and allergic diseases in community settings. Recent studies have established that mouse allergen is detectable in most US homes, with strikingly high levels in some inner cities. Inner city homes in major northeastern and midwestern US urban centers have levels as much as 100-fold higher than those found in other geographic regions. In addition, about 25% of inner city children with asthma have evidence of IgE sensitization to mouse. Several studies have shown that the combination of sensitization and exposure to higher levels of mouse allergen is associated with substantial asthma morbidity, including hospitalizations. Integrated pest management is efficacious in reducing mouse allergen levels and is recommended for sensitized patients with asthma. However, its impact on clinical outcomes has not yet been proven.

Introduction

Indoor allergens have long been understood to play an important role in the development of allergic sensitization and elicitation of symptoms in previously sensitized individuals. Historically, the most commonly studied indoor allergens have included dust mite, cockroach, and cat allergens; rodent allergens were primarily considered a source of occupational disease. However, over the past 5 to 10 years, there has been greater recognition of the important role that mouse and rat allergens have in the initiation and perpetuation of allergic disease in community settings. This review focuses on mouse and rat allergens and discusses their distribution and particle size characteristics, risk factors for high rodent allergen exposure, and the impact of exposure to these allergens on risk of allergic sensitization and asthma.

Rodent Allergens

Mouse urinary protein was first described about 25 years ago in the context of occupational studies [1]. Since then, allergens have been better characterized, standard allergen nomenclature has been applied, and the major allergen is now called Mus m 1. Mus m 1, a 16- to 19-kDa member of the lipocalin family, comes in many isoforms that generally vary from one another by only a handful of amino acid residues [2–4]. Mus m 1 serves as a pheromone-binding protein and is excreted in large quantities in mouse urine. Its expression is regulated by sex hormones. Male mice produce more Mus m 1 than female mice [5]. Mouse albumin is also both a urinary protein and an allergen, although it is a more minor allergen than Mus m 1 [6]. Mus m 2 also is described as a nonurinary allergen that is present in epithelium. Interestingly, Rat n 1, the major rat allergen, is also a lipocalin and pheromone-binding protein that is excreted in urine [7,8]. It shares 80% homology with Mus m 1, such that the coexistence of mouse and rat sensitization is observed in most, if not almost all, rodent-sensitized patients.

Distribution and Predictors of Exposure

The first studies to examine mouse allergen exposure were conducted in occupational settings. Typically, area or personal samples of airborne particles are collected and analyzed for Mus m 1 content. Sampling pumps are deployed that actively pull air through a filter that captures the airborne particles. Because the flow rate (liters per minute) and duration of sampling (minutes) are known, Mus m 1 exposure can be expressed as mass per volume of air, typically ng/m³. Using these methods, investigators described the particle size distribution in occupational settings and found that mouse allergen is carried predominantly on particles of less than 10 µm, such that it is readily deposited in airways [3]. Particle size in mouse rooms was larger than particle size in hallways and other areas outside of mouse rooms because smaller particles remain airborne longer and therefore travel greater distances than larger particles. Investigators have also evaluated predictors of higher mouse allergen levels in occupational settings and found that airborne mouse allergen levels are directly related to the mouse “load,” a measure of mouse density and ventilation in the room [3]. Higher humidity is associated with

Table 1. Mouse allergen exposure and sensitization by US geographic region

Setting	Detectable mouse allergen prevalence, %	Exposure levels, $\mu\text{g/g}$	Sensitization rate, %
Inner city			
Northeast/Midwest [19,24•,30•]	95–100	1–20+	11–46
South/West [24•]	37–64	0.001–1	8–20
Suburban housing [14,15]	75–82	0.007–0.36	13
Rural [28]	33*	–	12
*Report of mouse sighting.			

lower airborne mouse allergen levels, likely because moisture in the air enhances particle agglomeration, resulting in larger particles that are more likely to fall to dependent surfaces [9,10]. Caging systems and room ventilation also affect airborne mouse allergen levels [11,12]. In addition, substantial variability in airborne rodent allergens exists according to type of task performed by the laboratory animal worker, as well as across individuals performing the same task [13]. These findings have helped to provide industrial hygienists, clinicians, and other occupational health experts with insight into exposure reduction strategies that have successfully reduced airborne rodent allergen concentrations in animal facilities.

During the past decade, there has been great interest in home mouse allergen exposure, which has turned out to be widespread in US communities. For example, studies have shown that about 80% of US homes [14] and 75% of suburban Maryland homes [15] have detectable levels of mouse allergen. However, in some inner city communities, virtually 100% of homes have detectable mouse allergen [16–18]. Perhaps most importantly, levels in inner city homes are on the order of 100-fold higher than levels in suburban homes. The median Mus m 1 level in the kitchen in inner city homes ranges from 1.6 to 24.1 $\mu\text{g/g}$ [19] for US homes in general (median, 0.36 $\mu\text{g/g}$ [14]); for suburban Maryland homes, the median is 0.007 $\mu\text{g/g}$ [15]. The differences in concentrations of Mus m 1 are quite striking.

Not surprisingly, predictors of detectable levels of mouse allergen include reported problems with mice and evidence of mouse infestation in the home [16,17,20]. Other predictors that were identified by several studies include cockroach infestation and poor housing conditions—particularly holes or cracks in walls or doors, food remains in the home, older construction, poverty, and multifamily dwellings [14,16,17,20]. Patients often report acquiring a cat in an attempt to control mouse infestation. This inclination is supported by several studies that found an association between the presence of a cat and lower mouse allergen levels [9,14,20]. Mouse allergen levels vary by neighborhood [20]. Mouse allergen is also detected in school and daycare settings, with prevalence rates reflecting the prevalence rates in US homes [21–23].

Whereas occupational allergen exposure is typically assessed by quantifying the concentration of allergen in

airborne dust samples, home allergen exposure is typically assessed by quantifying the concentration of allergen in settled dust samples. Because exposure assessment methods differ between these two settings, it can be difficult to understand how the magnitude of allergen exposure in community settings relates to that in occupational settings, in which exposure is a known cause of allergic disease. One recent community-based study collected airborne dust samples from the bedrooms of inner city children with asthma and found that mouse allergen was detectable in air samples of 84% of the bedrooms [17]. Furthermore, 25% of homes had levels of at least 0.1 ng/m^3 , a concentration similar in magnitude to the lower range of concentrations found in occupational settings. In addition, airborne and settled dust samples were moderately correlated, indicating that on average, the higher the settled dust concentration, the higher the airborne concentration of mouse allergen. As is described in occupational settings, higher relative humidity is associated with lower airborne mouse allergen levels [9].

Home mouse allergen levels vary substantially by geographic region, as illustrated in Table 1. Major urban centers in the northeastern and midwestern United States have a higher prevalence of detectable mouse allergen and higher levels of mouse allergen [24•]. In cities such as Dallas, Tucson, and Seattle, mouse allergen is much less prevalent. A handful of international studies found generally lower levels and prevalence of mouse allergen, so it appears that mouse allergen may be less relevant outside the United States [25,26]. It is important then for health care providers to have an understanding of the geographic distribution of mouse allergen to understand whether exposure to this allergen is a likely contributor to their patients' allergic disease.

Investigators also have examined time-dependent changes in home mouse allergen levels. Not surprisingly, there is only a moderate correlation between a current mouse allergen level and levels 3 and 6 months in the future [9]. In fact, the more temporally distant the mouse allergen measurements are, the weaker the correlation is between them. Although both settled dust and airborne levels vary over time, airborne levels are more labile than settled dust levels. Mouse allergen levels also vary by season. Settled dust and airborne levels are lowest in the summer months, and airborne levels are highest in fall and winter. This sea-

sonal variation is likely a result of a combination of factors. For example, increased ventilation during warmer months because of open windows may result in lower allergen levels, particularly airborne levels. In addition, the tendency of mice to seek warm shelter in colder months may be at least partially responsible for increases in airborne allergen levels observed in fall and winter.

Rat allergen exposure in homes also was assessed, but only in studies of inner city children with asthma. Rat allergen was detected in 33% of inner city homes in the National Cooperative Inner-city Asthma Study and was associated with both rat and mouse infestation [8]. Airborne rat allergen in homes has not been quantified.

IgE Sensitization

Occupational studies indicate that about 20% of mouse workers have evidence of skin test sensitivity to mouse [27]. In suburban communities, the prevalence of mouse skin test sensitivity was estimated to be 12% to 13% [15,28]. In inner city children with asthma, prevalence rates of skin test sensitivity range from 11% to as high as 46% in some cities [18,29,30], which is higher than the prevalence in occupational settings. These sensitization prevalence rates are summarized in Table 1.

Although rodent contact in general was identified previously as a risk factor for IgE sensitization to rodents, more recent studies have attempted to describe the nature of the relationship between exposure and risk of sensitization more explicitly. In the National Cooperative Inner-city Asthma Study, a *Mus m* 1 level of greater than 1.6 µg/g was associated with an increased risk of mouse skin test sensitivity, and atopic predisposition further increased the risk of sensitization to mouse [29]. More recent studies examined the risk of IgE sensitization across a spectrum of exposure. In a suburban population, the prevalence of skin test sensitivity to mouse increased as settled dust mouse allergen levels increased, suggesting a monotonically increasing risk of sensitization with exposure [15]. However, in an inner city population in which mouse allergen levels were 100- to 1000-fold higher than those in the suburban population, risk of sensitization increased across the first three quartiles of exposure but was then attenuated at the highest levels of exposure [31]. This latter finding suggested that the highest exposure levels may afford some protection against IgE sensitization to mouse. The one community-based study that examined exposure-sensitization relationships for rat allergen found no relationship between home Rat n 1 levels and risk of IgE sensitization, but only 21% of the study population had a positive rat skin test [8].

Several studies have sought to determine if higher levels of rodent allergen exposure truly attenuate the risk of IgE sensitization, particularly within the occupational setting. Since the observation that higher cat allergen exposure was associated with an attenuated risk of IgE

sensitization to cat and higher cat-specific IgG levels [32], investigators interested in rodent allergen have started to examine the role of mouse- and rat-specific IgG responses in modifying the mouse- or rat-specific IgE response. In one cross-sectional study at the Jackson Laboratory, a mouse research and production facility, mouse-specific IgE and IgG responses increased monotonically with increasing exposure [27]. However, workers with the highest specific IgG4 levels had a lower prevalence of skin test sensitivity, suggesting that diversion of the antibody response to IgG4 from IgE may be one mechanism of protection against allergic sensitization [33]. Mouse-specific IgG antibodies may also play a role in protecting against the development of allergic symptoms in previously sensitized individuals. At the Jackson Laboratory, IgE-sensitized workers with the highest IgG and IgG4 levels had the lowest risk of mouse-associated allergic symptoms [34].

These findings were replicated for rat allergen. In a cross-sectional study of rat workers, the risk of IgE sensitization was attenuated among those who handled the greatest number of rats per day, but the prevalence of rat-specific IgG and IgG4 was highest among this group [35]. Those in this highest exposure group were also less likely to have rat-associated allergic symptoms than workers with lower rat exposure. Taken together, these studies suggest that rodent-specific IgG and IgG4 responses may modify the risk of IgE sensitization and the risk of allergic symptoms in previously IgE-sensitized individuals. However, all these studies were cross-sectional and therefore potentially biased. In addition, these studies used a range of methods to estimate exposure, which is another potential source of bias. Finally, these are epidemiologic observations for which immunologic mechanistic data are scant. Prospective studies that include examination of immunologic mechanisms and direct exposure measurements are needed to develop a better understanding of the interplay among rodent allergen exposure, humoral antibody responses, and allergic disease.

Clinical Relevance of Rodent Allergen Exposure

Laboratory animal allergy (LAA) and occupational asthma (OA) associated with rodent exposure in occupational settings are well described [4,5,36]. Allergic workers can have symptoms such as rhinoconjunctivitis, eczematous rashes, urticaria, and asthma. Disease surveillance is often used to detect incident cases of LAA and OA, and management of patients may include exposure reduction through use of respiratory protection or job reassignment and medication. Estimates indicate that 11% to 44% of laboratory animal workers will develop work-related allergic symptoms. Among workers who have allergic symptoms, about 4% to 22% will develop lower respiratory symptoms or have OA [37]. A more detailed discussion of LAA and OA can be found in other reviews focused on occupational allergic disease [37–39].

Table 2. Mouse allergen exposure/sensitization and respiratory outcomes

Population	Mouse/mouse allergen exposure	Mouse sensitization	Sensitization + exposure
Inner city children			
Incident wheeze	X [41]	X [42]	
Asthma morbidity			X [24•,30•]
Adults			
Asthma morbidity		X [43•]	
Asthma diagnosis	X [42]		

Recent studies have demonstrated that rodent allergen exposure in community settings is also clinically relevant. The impact of home rodent allergen exposure may not have been recognized previously because patients from nonoccupational settings are not likely to provide a history of symptoms with exposure because they generally do not have direct contact with mice. In addition, it may have been assumed that the degree of exposure resulting from living in a home with mouse infestation was much less than that resulting from handling rodents in an occupational setting. In the past 5 to 10 years, however, several studies have demonstrated a link between home mouse allergen exposure and a variety of respiratory outcomes. These findings are summarized in Table 2.

In a Boston birth cohort, mouse exposure in the first year of life was associated with an increased risk of wheeze in the first years of life, even after accounting for important confounders such as socioeconomic status. The role of allergic sensitization to mouse was not assessed as part of this report, so it is impossible to know whether mouse exposure resulted in allergic sensitization to mouse and then wheeze as a result of ongoing exposure, or whether mouse allergen exerts its effects on the lower respiratory tract through another mechanism [40,41]. In adult populations, mouse allergen exposure was associated with asthma diagnosis [42], and allergic sensitization to mouse was associated with more severe asthma among women [43•]. Mouse sensitization alone also is identified as a risk factor for allergic airways disease in young children. In a New York City birth cohort study, 2- to 3-year-old children with mouse sensitization were at much greater risk of wheeze, rhinitis, and eczema than those without mouse sensitization [44]. Furthermore, the higher the mouse-specific IgE level was, the greater the risk of wheeze and rhinitis. In this study, mouse allergen levels were measured but were not associated with risk of sensitization or risk of allergic disease. These studies together suggest that mouse sensitization is an important independent predictor of allergic respiratory disease in children and adults. One important point is that although these studies found a link between mouse sensitization and allergic disease, these relationships did not appear dependent on mouse allergen exposure. Two possible explanations for this finding are that mouse sensitization is also a surrogate measure for exposure (although one of these studies found no relationship between mouse sensitization and measured exposure)

or that mouse sensitization is a marker for burden of atopy, which is associated with asthma severity.

However, some studies have found that the combination of mouse sensitization and exposure (not sensitization or exposure alone) is associated with worse asthma outcomes. In two recent studies, mouse-sensitized inner city children who were exposed to higher levels of mouse allergen had worse asthma across a number of measures of morbidity. In a Baltimore City preschool population, about one quarter of children had evidence of IgE sensitization to mouse. Those who had greater than 0.5 µg/g of Mus m 1 in a bedroom settled dust sample had more days of symptoms, short-acting β-agonist use, cough without a cold, and exercise-related symptoms than nonsensitized children or children with lower exposure [30•]. In addition, the sensitized and exposed children had a twofold to threefold increased risk of an unscheduled physician or emergency department visit for asthma compared with nonsensitized or less exposed children. Furthermore, the sensitized and exposed children were at much greater risk for hospitalization for asthma. These findings were replicated in the Inner-city Asthma Study (ICAS), a multicenter study of school-age children with asthma. In ICAS, 22% of children had a positive skin test to mouse, and children with higher bedroom Mus m 1 levels were at greater risk for asthma morbidity [24•]. One important difference between these two studies is that there is a 10-fold difference in cut points of mouse allergen exposure that are associated with morbidity, with the ICAS finding an association between asthma morbidity and much lower Mus m 1 levels than the Baltimore study. There are several potential explanations for this, the most likely of which has to do with the underlying distribution of mouse allergen exposure in the respective study populations, which can influence the location of the allergen exposure cut point for morbidity outcomes. Ultimately, studies that examine relationships between morbidity and the full spectrum of mouse allergen exposure are needed to develop a better understanding of this relationship and to determine how best to modify exposure to affect improvements in morbidity.

One study examined the relationship of rat allergen exposure to asthma morbidity in inner city children with asthma. A total of 21% of the children had a positive rat skin test, and 33% of the homes had detectable rat allergen [8]. The authors found that the presence of detectable

rat allergen was associated with a higher risk of hospitalization and unscheduled physician visits for asthma among rat-sensitized children.

These recent findings underscore the importance of assessing rodent sensitization in children with asthma, particularly those from underserved urban communities. A positive skin prick test or mouse urine-specific IgE test has a high positive predictive value for having allergic symptoms with nasal challenge, suggesting that these currently available diagnostic tests provide clinically meaningful information [45]. Although collection of home settled dust samples for allergen analysis is generally not feasible for the clinician, obtaining a history of mouse sightings from parents or caregivers can provide some meaningful information about home mouse allergen exposure. Parent report of recent mouse sightings is a strong predictor of higher levels of home mouse allergen levels, and one study found that parent report of mice had a 90% positive predictive value for mouse allergen levels greater than 0.5 µg/g [46]. Denial of mouse sightings or infestation, however, does not provide reassurance that home mouse allergen levels are low, so we cannot rely on this to rule out clinically relevant mouse allergen exposure in a patient's home.

Environmental interventions aimed at reducing home mouse allergen levels—specifically integrated pest management (IPM)—should be recommended for asthma patients with evidence of IgE sensitization to mouse. IPM consists of multiple strategies aimed at eliminating mice, reducing food sources for mice, and preventing entry of mice into the home. Setting traps, cleaning up crumbs and other food remains, storing foods in plastic containers through which mice cannot chew, and sealing holes and cracks in the home are some IPM strategies for mouse infestation. In fact, an IPM approach was successful in reducing home mouse allergen levels by 75% in one pilot study [19]. In this study, a pest management expert inspected the homes to target traps to areas of recent mouse activity, and a rodenticide was applied to areas that were out of reach of children and pets. An important caveat is that this IPM intervention was designed and applied by a rodent management expert. Thus, the efficacy of rodent control measures applied by commercial pest control companies is unknown. In fact, one rodent intervention study in which research assistants educated families to practice IPM demonstrated only a 27% decrease in mouse allergen levels overall. However, among the subgroup in which rodent allergen levels dropped by at least 50%, there was less missed school and sleep reduction, suggesting some effect on asthma [24•]. Another potential strategy for mouse allergen abatement is the use of air filtration. Although the efficacy of air filtration in reducing other airborne animal allergens—specifically cat and dog—has been studied, findings have been mixed at best [47,48]. However, these studies have tested the efficacy of air filtration while the furred pet—the source of the allergen—has remained in the home. Air filtration may have a role as an adjunct to IPM for mouse allergen abatement, but this has yet to be studied.

Conclusions

Mouse allergen is an important contributor to nonoccupational allergic respiratory disease, particularly in underserved urban populations. Assessing mouse sensitization in patients with asthma and other allergic diseases is an important part of the clinical evaluation of such patients. Sensitized patients should be asked about recent signs of mouse infestation and educated about IPM approaches to reduce mouse allergen levels.

Disclosure

No potential conflict of interest relevant to this article was reported.

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