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Mouse allergen exposure is associated with decreased risk of allergic rhinitis in school-aged children

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Introduction

Allergic rhinitis (AR) affects up to ~14% of adults[1] and ~22% of children[2] in the United States, and its prevalence can be as high as 60-80% among children with asthma[3,4]. In Europe, a large multi-center study that combined survey and physical examination data reported that AR affects ~13-23% of the population[5]; that study reported up to ~45% under-diagnosis. We recently reported up to ~75% AR under-diagnosis among Puerto Rican (PR) children[6], who bear a disproportionate burden of asthma[7].

The presence and severity of AR have been associated with several comorbidities in children, including asthma, otitis media, and adenoid hypertrophy[8]. It has also been associated with higher risk of chronic sinusitis in adults[9]. AR may worsen asthma severity and control by enhancing lower airway inflammation[10] and may delay recovery of lung function after asthma exacerbations[11]. Adequate treatment with nasal corticosteroids may improve lung function in children with asthma[12], although some studies have shown no improvement on asthma-related airway inflammation[13].

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Exposure to higher levels of mouse urinary protein (Mus m 1, hereinafter called 'mouse allergen') has been previously linked with mouse sensitization and indicators of asthma severity or control in some studies[14,15] but not in others[16,17]. To date, little is known about the association between mouse allergen exposure and allergic rhinitis (AR). We hypothesized that mouse allergen exposure would be associated with decreased prevalence of AR in PR children, and explored potential mechanisms by analyzing possible correlated microbe-associated molecular patterns (MAMPs).

Methods

Study Population

The details of the study recruitment and protocol have been previously described[6,18,19]. In brief, from March 2009 to June 2010, children in San Juan (Puerto Rico) were chosen from randomly selected households using a multistage probability sample design scheme similar to that of a prior study[20]. Primary sampling units (PSUs) were randomly selected neighborhood clusters based on the 2000 U.S. census, and secondary sampling units were randomly selected households within each PSU. A household was eligible if one or more residents was a child aged 6 to 14 years. In households with more than one eligible child, one child was randomly selected for screening[20]. After selection and screening, we attempted to enroll a total of 783 children. Parents of 105 of these 783 eligible households refused to participate or could not be reached; there were no significant differences in age, sex, or area of residence between eligible children who did (n=678, ∼87%) and did not (n=105, ∼13%) agree to participate. For the current study, focused on allergic rhinitis and mouse allergen exposure, only those with non-missing data on allergy skin testing and Mus m 1 levels (n=511) were included; there were no significant differences between those included and those excluded from analysis (n=167) (see eTable 1 in the E-Supplement). Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Jan, PR), Brigham and Women's Hospital (Boston, MA), and the University of Pittsburgh (Pittsburgh, PA).

Study Procedures

Study participants completed a protocol that included questionnaires, allergy skin testing, and collection of dust samples. The child's parents completed two questionnaires used in the Genetics of Asthma in Costa Rica Study[21]. These questionnaires were used to obtain information about the child's general and respiratory health, family history, socio-demographic characteristics, in utero smoke exposure, family history, and household characteristics.

Skin test reactivity (STR) to aeroallergens, histamine and saline diluent, was assessed using a Multi Test device (Lincoln Diagnostics, Decatur, IL) on the skin of the forearm (in a site free of eczema). Aeroallergens tested included house dust mites (*D. pteronyssinus* and *D. farinae*), *B. tropicalis*, German cockroach (*B. germanica*), mouse pelt, dog dander, cat dander, mold mix, *Alternaria tenuis*, mixed tree pollen, mixed grass pollen, mugwort sage,

and ragweed (Alk-Abello, Round Rock, TX). A skin test was considered positive if the maximum wheal diameter exceeded the diluent wheal diameter by ≥3 mm.

Dust samples were obtained from three areas in the home: the one in which the child sleeps (usually his/her bedroom), the living room/television room, and the kitchen. The dust was sifted through a 50-mesh metal sieve, and the fine dust was reweighed, extracted, and aliquoted for analysis of allergens from mouse (mouse urinary protein [Mus m 1]), dust mite (*Dermatophagoides pteronyssinus* [Der p 1]), cockroach (*Blatella germanica* [Bla g 2]), dog dander (Can f 1), and cat dander (Fel d 1), as well as microbe-associated molecular patterns (MAMP) levels of glucan, peptidoglycan and endotoxin (see E-Supplement for details). Levels of allergens and MAMPs were transformed to a log-10 scale for analysis, and are reported as geometric means for clarity.

Outcome Definition

AR was defined by having both current symptoms suggestive of AR and STR to ≥1 allergen; this definition is consistent with Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 guidelines[22]. A child was considered to have current symptoms suggestive of AR if there were affirmative answers to two questions (taken from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire[23]): 1) “Has your child ever had hay fever or a runny or stuffy nose accompanied by sneezing and itching at a time when he/she did not have a cold or flu?”, and 2) “Has your child had these symptoms in the last 12 months?”. Asthma was defined as physician-diagnosed asthma and wheeze in the previous year.

Statistical Analysis

Bivariate analyses were conducted using Fisher's exact tests for categorical variables, and two-sample two-sided *t* tests for continuous variables. Logistic regression was used for the multivariable analyses. Because of their known relation to AR, all models included age, sex, and type of health insurance (private/employer-based vs. others). Other covariates (see Table 1) were also included in the initial multivariate models if $p \leq 0.20$ in bivariate analyses; these additional covariates remained in the final models if they were associated with AR at $p < 0.05$ or if they changed the parameter estimates by ≥10%. The Pearson correlation coefficient was used to assess the relationship between levels of MAMPs and mouse allergen. Parental education was dichotomized into at least one parent completed high school vs. none. Household income was dichotomized into above or below $15,000/year, as that was the approximate median income in Puerto Rico during the study. Eczematous rash referred to ever having a prolonged, itchy, scaly or weepy skin rash. All analyses were done using Stata/SE 12.1 (College Station, TX).

Results

The characteristics of participants (n=511) who did and did not have AR is shown in Table 1. AR was present in 247 (48.3%) of participating children. Variables significantly and positively associated with AR included asthma, an eczematous rash, parental AR, parental asthma, history of daycare, reported signs of mold/mildew in the home, STR ≥1 allergen, total number of positive skin tests, and STR to dust mite, *B. tropicalis*, cockroach, mouse,

dog, cat, *Alternaria*, mixed trees, mixed grasses, mugwort sage and ragweed. Mus m 1 and shared bedroom were significantly and inversely associated with AR.

Table 2 shows the multivariate analysis of mouse allergen exposure and AR. After adjustment for age and sex (Model 1A in Table 2), private/employer-based health insurance and asthma were significantly associated with increased odds of AR, whereas Mus m 1 level and shared bedroom were significantly associated with decreased odds of AR: each $\log_{10}$-unit increment in Mus m 1 level decreased the odds of AR by 25% (95 confidence interval [CI] = 8% - 38%). Among children sensitized to mouse (Model 1B in Table 2), there was a similar trend for a reduction in the odds of AR with increasing Mus m 1 level, though it did not reach statistical significance (p=0.15); and asthma was still associated with increased odds of AR. Among children not sensitized to mouse (Model 1C in Table 2), Mus m 1 level was significantly associated with decreased odds of AR after adjustment for relevant covariates: each $\log_{10}$-unit increase in Mus m 1 level decreased the odds of AR by ∼21% (95% CI = 1% - 37%). Since asthma was such a strong predictor of AR in our sample, we then explored whether there was an interaction between mouse allergen and asthma on AR, without significant results (data not shown).

Given that prior studies have shown an inverse association among exposure to microbial components and asthma or allergic sensitization[24], we then investigated whether findings for mouse allergen and AR were due to correlated microbial components detected in house dust (endotoxin, peptidoglycan and glucan). Figure 1 shows scatterplots for glucan, peptidoglycan, and endotoxin vs Mus m 1. Of the three, only endotoxin was significantly correlated with Mus m 1 ($r=0.184$, $p<0.001$).

In light of this correlation, we added ($\log_{10}$-transformed) endotoxin levels to the multivariable models of mouse allergen and AR (see Models 2A-2C in Table 2). In these models, endotoxin was not significantly associated with AR among all subjects (Model 2A) nor in the subgroups of children sensitized (Model 2B) or not sensitized (Model 2C) to mouse. Adding endotoxin to the models also did not affect the inverse association between Mus m 1 level and AR, although interestingly it did decrease the parameter estimates for asthma by >10%.

Discussion

To the best of our knowledge, this is the first study looking at the association between mouse allergen level and allergic rhinitis in children. We report that exposure to higher levels of mouse allergen are associated with decreased odds of AR, and that these results are driven by children who are not sensitized to mouse.

Exposure to mouse allergen has been linked to increased odds of atopic sensitization, predominantly in inner-city or urban environments[16,25]. In a cohort of children with parental history of allergy or asthma, Phipatanakul *et al.* reported that exposure to detectable levels of Mus m 1 in home dust at 2-3 months of age was associated with a twofold increase in the odds of allergic sensitization by age 7 years, compared to those with non-detectable levels[25]. Recently, the presence of anti-mouse IgE at 3 years of age was found to be associated with

increased risk of wheeze, rhinitis, and atopic dermatitis. Thus, studies to date have reported relationships between allergen level and sensitization, and between sensitization and AR or asthma[26]. Our results suggest that exposure to mouse allergen levels in children who do not develop mouse sensitization may actually have a protective effect against the development of AR, with a ~21-25% reduction in the odds of AR per each $\log_{10}$-unit increase in house dust Mus m 1 level. This is consistent with our previous report that higher levels of mouse allergen are associated with better lung function among asthmatic children who are not sensitized to mouse[17]. We speculate that exposure to mouse allergen –or an associated factor– may exert protective, immune-modulatory effects among children who are not allergic to it; whereas this protective effect is lost among children who become allergic to mouse. However, given the smaller number of sensitized vs. non-sensitized children, we cannot fully rule out lack of statistical power to detect an association in the sensitized group.

Based on all of this, we initially hypothesized that mouse allergen level might be a proxy for exposure to other microbial exposures in these children. However, when evaluating the correlation between Mus m 1 and several MAMPs, only endotoxin was significantly (albeit weakly) correlated, and its inclusion in our models did not affect the significance or magnitude of the association between Mus m 1 and AR. Future studies will be needed to elucidate mechanisms by which exposure to mouse allergen may be indeed protective for AR or asthma, or if perhaps certain characteristics of these children make them less likely to develop mouse sensitization and also less prone to developing AR.

Levels of mouse allergen in our study had a mean of 290ng/g (0.29μg/g) and ranged from undetectable (n=58) to 31,227ng/g (or ~4.5 $\log_{10}$). While these levels are lower than those reported in similar studies performed in inner cities in the U.S. –particularly those from the Northeast– prior studies have found similar variability: one study in Boston reported up to 68% of households had Mus m levels <0.25μg/g[25], while other inner-city studies have reported medians of ~0.3-0.4μg/g[27,28]. It will be important to determine whether differences in the level of exposure may modify the effect reported. We hypothesize that in environments with relatively low ranges of Mus m 1 levels, the ‘beneficial’ effect among non-sensitized children may predominate (with no effect seen among sensitized children)[17], whereas in environments with higher levels of exposure, the ‘deleterious’ effect among sensitized children prevails (with ‘no effect’ detected among non-sensitized children)[29,30].

We must acknowledge several limitations. Firstly, the cross-sectional design of the study precludes assessment of temporal relationships between mouse allergen levels and the outcomes assessed. However, positive determinants of mouse allergen load, including urban neighborhoods, lower income homes, older homes, household characteristics and practices[31], may all be relatively stable from early-life throughout childhood. This is in contrast to pet ownership, which may be more susceptible to disease-associated modification of exposure. Secondly, we focused on PR children due to their disproportionate burden of asthma and atopy[7] and the range of mouse allergen level was lower than those reported elsewhere, as previously discussed. However, mouse allergen is ubiquitous in inner-city homes in the United States[16,32], and thus our findings are likely applicable to those environments and its under-served populations. Thirdly, while we adjusted for multiple potential confounders, there may be unmeasured factors at least partly responsible for these

results. Of note, additionally adjusting for dust mite (*D.pteronyssinus*) allergen level and family history of AR did not change our results (data not shown).

In summary, mouse allergen level was inversely associated with AR in PR children, independently of levels of endotoxin in house dust, and the results were driven mainly by children not sensitized to mouse. This finding could be explained by early-life induction of tolerance by mouse allergen or by microbes that are present in mouse feces but were not measured in this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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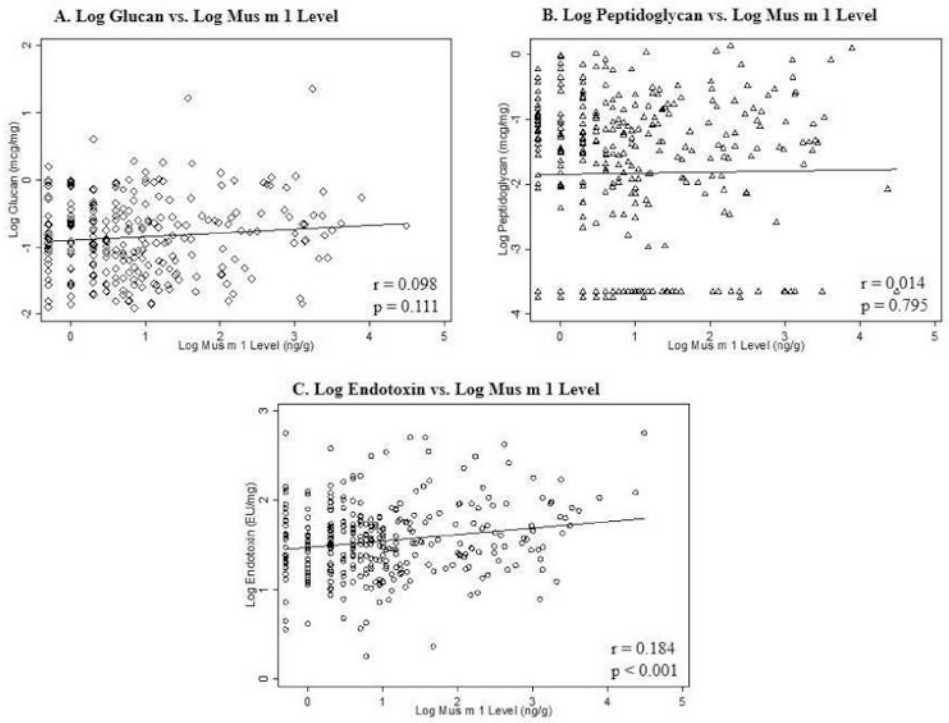

Figure 1. Scatterplots of Microbe-Associated Molecular Patterns (MAMPs) vs. Mus m 1

Log_{10} microbe-associated molecular patterns and log_{10} Mus m 1 levels are plotted with regression lines. Pearson correlation coefficient (r) and associated p-values are shown for each plot.

Table 1
Characteristics of Study Participants

	No AR (n = 264, 51.7%)	AR (n = 247, 48.3%)
Baseline characteristics		
Age (years)	10.2 (9.9, 10.5)	10.5 (10.1, 10.8)
Female sex	126 (47.7%)	113 (45.8%)
Parental education (>high school)	205 (77.7%)	204 (82.6%)
Higher household income (>$15K/year)	80 (31.6%)	89 (36.8%)
Private/employer-based health insurance	77 (29.2%)	94 (38.1%)*
Asthma	92 (34.9%)	176 (71.3%)**
Leukotriene inhibitor in prior 6 months	19 (7.2%)	49 (19.8%)**
Inhaled corticosteroids in prior 6 months	24 (9.1%)	64 (25.9%)**
Atopic history		
Eczematous rash, ever	59 (22.4%)	104 (42.1%)**
Family history		
Parental history of allergic rhinitis	40 (15.2%)	57 (23.2%)*
Parental history of asthma	111 (42.2%)	145 (58.7%)**
Parental history of eczema	4 (1.5%)	8 (3.3%)
Home environment		
Number of older siblings	1.8 (1.6, 2.0)	1.6 (1.4, 1.8)
Shared bedroom	155 (58.7%)	121 (49.0%)*
History of daycare	48 (18.3%)	63 (25.9%)*
Signs of mold/mildew	88 (33.5%)	119 (48.2%)**
Dog at home	132 (50.4%)	131 (53.0%)
Cat at home	32 (12.3%)	21 (8.5%)
Seeing rats or mice	81 (30.7%)	57 (23.1%)
Skin test reactivity		
≥1 allergen	143 (54.2%)	247 (100.0%)**
Total number positive skin tests	2.8 (2.3-3.3)	5.6 (5.1-6.0)**
Dust mite mix	47 (17.9%)	108 (43.9%)**
B. tropicalis	81 (31.5%)	179 (73.7%)**
Cockroach	47 (18.0%)	106 (43.6%)**
Mouse	39 (14.8%)	72 (29.2%)**
Dog	42 (15.9%)	82 (33.2%)**
Cat	68 (25.8%)	103 (41.7%)**
Mold mix	25 (9.5%)	37 (15.0%)
Alternaria	44 (16.7%)	75 (30.4%)**
Mixed trees	59 (22.4%)	83 (33.6%)*

	No AR (n = 264, 51.7%)	AR (n = 247, 48.3%)
Mixed grasses	28 (12.2%)	49 (21.9%)*
Mugwort sage	22 (9.6%)	43 (19.8%)**
Ragweed	73 (27.7%)	131 (53.0%)**
Home allergen levels[1]		
Log Der p (μg/g)	4.2 (3.7, 4.9)	4.8 (4.1, 5.5)
Log Bla g 2 (U/g)	1.9 (1.6, 2.3)	1.8 (1.5, 2.2)
Log Mus m 1 (ng/g)	12.7 (9.7, 16.6)	8.5 (6.3, 11.4)*
Log Can f 1 (μg/g)	0.19 (0.15, 0.25)	0.16 (0.12, 0.21)
Log Fel d 1 (μg/g)	0.04 (0.03, 0.06)	0.03 (0.02, 0.04)
Microbial associated molecular patterns[1]		
Log glucan (μg/mg)	0.14 (0.11, 0.17)	0.15 (0.12, 0.19)
Log peptidoglycan (μg/mg)	0.014 (0.009, 0.02)	0.015 (0.01, 0.02)
Log endotoxin (EU/mg)	34.8 (30.6, 39.6)	36.2 (31.1, 42.2)

Values are presented as number (%) or mean (95% CI).

[1] Presented as geometric means (95% CI). Difference between subjects with and without AR on univariate analysis at

* P<0.05,

** P<0.005.

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Table 2

Multivariate analysis of mouse allergen level and AR by mouse sensitization status

All Subjects	**Unadjusted (n = 511)**		**Adjusted Model 1A (n = 511)**		**Adjusted Model 2A (n = 328)**	
	OR (95% CI)	**P-val**	**OR (95% CI)**	**P-val**	**OR (95% CI)**	**P-val**
Mus m 1 (ng/g)[1]	0.84 (0.70, 1.00)	.049	0.75 (0.62, 0.92)	.005	0.72 (0.57, 0.92)	.009
Endotoxin[1]	1.11 (0.64, 1.92)	.703	---	---	1.22 (0.66, 2.24)	.528
Health insurance type	1.49 (1.03, 2.16)	.034	1.66 (1.10, 2.52)	.017	1.61 (0.91, 2.83)	.100
Asthma	4.63 (3.19-6.74)	<.001	6.40 (4.20, 9.73)	<.001	5.08 (3.01, 8.59)	<.001
Shared Bedroom	0.68 (0.48, 0.96)	.028	0.50 (0.33, 0.76)	.001	0.44 (0.26, 0.73)	.002
Sensitized to Mouse	**Unadjusted (n = 111)**		**Adjusted Model 1B (n = 111)**		**Adjusted Model 2B (n = 76)**	
Mus m 1 (ng/g)[1]	0.78, 0.52, 1.19)	.256	0.71 (0.44, 1.13)	.150	0.79 (0.41, 1.51)	.470
Endotoxin[1]	0.83 (0.28, 2.52)	.748	---	---	0.89 (0.26, 3.05)	.858
Health insurance type	0.94 (0.41, 2.15)	.881	0.99 (0.39, 2.50)	.976	0.86 (0.24, 3.12)	.823
Asthma	4.79 (2.07, 11.12)	<.001	6.56 (2.48, 17.37)	<.001	4.62 (1.48, 14.47)	.009
Shared Bedroom	0.78 (0.35, 1.71)	.531	0.61 (0.24, 1.52)	.286	0.63 (0.21, 1.96)	.428
Not Sensitized to Mouse	**Unadjusted (n = 400)**		**Adjusted Model 1C (n = 400)**		**Adjusted Model 2C (n = 252)**	
Mus m 1 (ng/g) [1]	0.88 (0.72, 1.07)	.204	0.79 (0.63, 0.99)	.040	0.74 (0.56, 0.98)	.033
Endotoxin[1]	1.27 (0.66, 2.44)	.475	---	---	1.42 (0.68, 2.95)	.344
Health insurance type	1.72 (1.13, 2.61)	.011	1.97 (1.22, 3.17)	.005	2.10 (1.10, 4.02)	.025
Asthma	4.80 (3.12, 7.37)	<.001	6.84 (4.21, 11.14)	<.001	5.54 (2.96, 10.38)	<.001
Shared Bedroom	0.64 (0.43, 0.95)	.026	0.44 (0.27, 0.72)	.001	0.35 (0.19, 0.65)	.001

All models adjusted for age, sex, and variables listed; model 2 additionally adjusted for endotoxin level (EU/mg).

[1] Per each $\log_{10}$ unit increment.