Physician-diagnosed eczema is an independent risk factor for incident mouse skin test sensitization in adults

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ABSTRACT

Background: The disrupted skin barrier in eczema has been associated with an increased risk of immunoglobulin E (IgE) sensitization in childhood. However, it is unclear whether eczema, independent of atopy, is a risk factor for the development of allergic sensitization in adulthood.

Objective: To determine if skin barrier dysfunction, independent of atopy, is a risk factor for incident sensitization in adult workers at a mouse production and research facility.

Methods: New employees at The Jackson Laboratory enrolled in a cohort study and underwent skin-prick testing (SPT) at baseline and every 6 months to mouse and to a panel of aeroallergens (net wheal ≥ 3 mm indicated a positive SPT result). Mouse allergen exposure was measured every 6 months by using personal air monitors. Physician-diagnosed eczema was defined as self-reported physician-diagnosed eczema. Cox proportional hazard modeling was used to examine the association between baseline physician-diagnosed eczema and incident mouse skin test sensitization and adjusted for potential confounders.

Results: The participants (N = 394) were followed up for a median of 24 months. Fifty-four percent were women, 89% were white, and 64% handled mice. At baseline, 7% of the participants reported physician-diagnosed eczema and 9% reported current asthma; 61% had at least one positive skin test result. At 30 months, 36% of those with eczema versus 14% of those without eczema had developed a positive mouse skin test result ($p = 0.02$, log-rank test). After adjusting for age, race, sex, smoking status (current, former, never), current asthma, hay fever, the number of positive SPT results at baseline, and mouse allergen exposure, physician-diagnosed eczema was an independent risk factor for incident mouse SPT sensitization (hazard ratio 5.6 [95% confidence interval, 2.1–15.2]; $p = 0.001$).

Conclusion: Among adult workers at a mouse production and research facility, physician-diagnosed eczema was a risk factor for incident mouse sensitization, independent of atopy, which indicated that a defect in skin barrier alone may increase the risk of skin sensitization, not just in childhood, but throughout life.

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Allergic sensitization is common¹ and is a risk factor for allergic disease. Exposure *via* skin, particularly a dysfunctional skin barrier, has been a proposed mechanism for immunoglobulin E (IgE) sensitization.² Early onset eczema has been associated with an increased IgE sensitization risk.³ Whether eczema, as a marker of skin barrier dysfunction, is a risk factor for sensitization in adults, independent of atopy, remains unclear. A unique model for studying risk factors for incident

sensitization is laboratory animal allergy. Laboratory animal workers are at high risk for development of laboratory animal allergic sensitization and/or allergy,⁴ and animal allergen exposure and sensitization can be repeatedly measured, which provides a unique opportunity to understand risk factors and mechanisms of allergic sensitization. We, therefore, examined the association between eczema in adults at the start of employment and the risk of incident mouse sensitization in the JAXCohort Study.⁵

METHODS

The JAXCohort Study⁵ was a prospective cohort study of new employees ages ≥ 18 years at The Jackson Laboratory who were followed up from 2004 to 2014 and who underwent repeated skin-prick testing (SPT). Study participants who had a negative mouse SPT result at baseline and at least 6 months of follow up were included in the analysis population for this study. Mouse is the only laboratory animal at The Jackson Laboratory. Of the 465 participants in the cohort, a total of 394 participants were included in the analysis pop-

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ulation for incident SPT sensitization; 18 participants were excluded for having a positive mouse SPT result at baseline, and 53 participants were excluded who did not have at least 6 months of follow up.

The JAXCohort study was approved by institutional review boards at the Johns Hopkins Medical Institutions and The Jackson Laboratory.⁵ Sociodemographic data; smoking history; and medical history, including allergic and pulmonary history, were collected at baseline by trained study staff *via* questionnaire. The interval histories, including allergic and occupational history, were collected every 6 months by questionnaire. SPT was performed by using the MultiTest II device (Lincoln Diagnostics, Decatur, IL) at baseline to mouse, rat, cat, dog, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, pine, birch, oak, orchard grass, *Alternaria*, *Aspergillus*, *Penicillium*, and ragweed, and, every 6 months, to mouse, rat, cat, dog, dust-mite mix, and pine. Blood was collected every 6 months for measurement of mouse-specific IgE (e72, ImmunoCAP; ThermoFisher, Uppsala, Sweden). Mouse allergen exposure was measured every 6 months by personal air monitoring, as previously described.⁵

Chronic, itchy rash was ascertained by the question "Have you ever had an itchy rash which was coming and going for at least 6 months?" from the International Study of Asthma and Allergies in Childhood eczema questionnaire.⁶ Physician-diagnosed eczema was defined as self-report of having a physician diagnosis of eczema. Mouse skin test positivity was defined as a net SPT result wheal ≥ 3 mm; mouse IgE positivity was defined as mouse-specific IgE levels of ≥ 0.35 kU/L (e72, ImmunoCAP). Statistical analyses were performed by using Stata 13, SE (StataCorp, LLC, College Station, TX). A *p* value of <0.05 was considered statistically significant. Kaplan-Meier survival plots and the log-rank test were used to estimate the time to mouse positivity and to test the effect of eczema on incident mouse sensitization outcomes. Cox proportional hazard models of the relationships between eczema at baseline and the time to mouse sensitization were adjusted for age, sex, race, smoking status (current, former, never), current asthma, hay fever, number of positive SPT results at baseline, and mouse allergen exposure.

RESULTS

A total of 394 participants were included in the analysis population for incident mouse SPT sensitization. The participants were followed up for a median of 24 months; the mean age was 32 years, 54% were women, 89% were white, and 64% handled mice (Table 1). At baseline, 12.5% reported having had a chronic, itchy rash, and 7% reported physician-diagnosed eczema. Nine percent reported current asthma, and 61% had at

Table 1 Analysis population characteristics (N = 394)

Age, mean $\pm$ SD, y	32.3 $\pm$ 10.2
Men, no. (%)	179 (45.6)
Race/ethnicity, no. (%)	
White	351 (89.3)
Asian	33 (8.4)
Other	9 (2.3)
Eczema, no. (%)	
Chronic, itchy rash	49 (12.5)
Physician-diagnosed eczema	26 (7.0)
Other atopic disorders, no. (%)	
Hay fever	69 (17.6)
Current asthma	37 (9.4)
SPT sensitization, no. (%)	
≥ 1 SPT result	240 (61.1)
SPT results, mean $\pm$ SD, no.	1.8 $\pm$ 2.0
Dust mite	170 (45.0)
Pollen	143 (36.4)
Cat	54 (13.7)
Dog	10 (2.5)
Follow up, median, mo	24
Mouse exposure	
Handled mice, no. (%)	249 (63.7)
Personal airborne Mus m 1, median (IQR), ng/m ³	0.80 (0.68–0.91)
Smoking status, no. (%)	
Current	86 (21.9)
Former	82 (20.9)
Never	225 (57.2)

SD = Standard deviation; SPT = skin-prick test; IQR = interquartile range; Mus m 1 = major mouse allergen.

least one positive skin test result. Overall, 53 of the participants (13.5%) with a negative baseline mouse SPT result developed a positive mouse SPT result during the follow-up period and 20 of the participants (5.0%) with a negative mouse-specific IgE level result developed a positive mouse-specific IgE level result during the follow-up period. At 30 months of the follow-up time, 36% of those with physician-diagnosed eczema versus 14% of those without physician-diagnosed eczema had developed a positive mouse skin test result (*p* = 0.02, log-rank test) (Fig. 1 A). There was no difference between the eczema groups in incident mouse-specific IgE levels (Fig. 1 B).

After adjusting for age, race, sex, smoking status, current asthma, hay fever, number of positive skin test results at baseline, and mouse allergen exposure, physician-diagnosed eczema was an independent risk factor for incident mouse SPT sensitization (hazard ratio 5.6 [95% confidence, 2.1–15.2]; *p* = 0.001) (Table 2). Additional adjustment for self-report of personal res-

Figure 1. Kaplan-Meier plots of (A) time to positive mouse SPT and (B) time to positive mouse IgE, by physician-diagnosed eczema. Solid line = participants without a physician diagnosis of eczema, Dashed line = participants with a physician diagnosis of eczema, p-value shown is for the log-rank test statistic.

pirator use attenuated the effect of physician-diagnosed eczema, but the association with incident mouse SPT sensitization was still present (Table 3). Sixty-one of the participants (15.9%) not sensitized to mouse at baseline developed a positive mouse SPT result or increased mouse-specific IgE level during the follow-up period.

Thirty-eight percent of those with physician-diagnosed eczema versus 16% of those without physician-diagnosed eczema became mouse sensitized, defined as either a SPT result net wheal of ≥ 3 mm or mouse-specific IgE level of ≥ 0.35 kU/L, by 30 months ($p = 0.04$, log-rank test) (Fig. 2). After adjusting for age, race, sex, smoking status (current, former, never), current asthma, hay fever, number of positive SPT results at baseline, and mouse allergen exposure, physician-diagnosed eczema was an independent risk factor for incident mouse sensitization (hazard ratio 5.2 [95% confidence interval, 1.6–10.9]; $p = 0.003$) (Table 2). When we examined incident cat, dog, dust mite, rat, and pine sensitization, we found that chronic, itchy rash was a risk for incident cat skin test sensitization ($p = 0.02$, log-rank test). We found no association between chronic, itchy rash and physician-diagnosed eczema and dog, dust mite, rat, and pine sensitization.

DISCUSSION

We examined the relationship between eczema in adults and the risk of incident mouse sensitization in a prospective occupational cohort study of employees who worked with mice, which provides a unique model for studying risk factors for incident aeroallergen exposure. In this study population, physician-diagnosed eczema was a risk factor for mouse SPT sensitization, independent of multiple measures of atopy, including current asthma, hay fever, and number of baseline positive skin test results. These findings indi-

cated that skin barrier dysfunction may be a risk factor for aeroallergen sensitization throughout life, not just in infancy, and are consistent with previous reports of associations between filaggrin gene defects and an increased risk of allergic sensitization.²

It is not clear why there was an association between physician-diagnosed eczema and incident mouse skin test sensitization but not incident mouse-specific IgE sensitization. Previous reports of filaggrin gene defects and an increased risk of allergic sensitization often only report on serum-specific IgE or SPT,² or use the term sensitization to encompass both outcomes. One possible explanation of the discordant findings between the two mouse sensitization outcomes is that mouse SPT may be more sensitive than mouse-specific IgE testing, particularly in a population just developing sensitization. Another possible explanation is that the skin, with its own skin-associated lymphoid tissue, may have the capacity for local IgE production, similar to the observation that local nasal IgE can be found in individuals with classic allergic symptoms but no evidence of systemic allergen-specific IgE.⁷ Future studies should examine if the route of allergen exposure influences restriction of IgE to a particular end organ or compartment.

Self-report of a chronic, itchy rash at baseline, in contrast to physician-diagnosed eczema, was not associated with an increased risk of mouse skin test sensitization. Slightly more than one-third of the participants who reported a chronic, itchy rash also reported physician-diagnosed eczema, a proportion consistent with previously reported population-level survey data,⁸ which indicated that reporting of physician-diagnosed eczema may be a marker of more severe or extensive disease. More severe and/or extensive disease may be a marker of filaggrin mutations⁹ and/or

Table 2 Associations between chronic, itchy rash vs. physician-diagnosed eczema and incident mouse sensitization

Risk Factor	Mouse Sensitization Outcome, HR (95% CI); <i>p</i> Value*					
	Positive SPT Result			Positive IgE Level		
	Crude	Adjusted#	Crude	Adjusted#	Crude	Adjusted#
Chronic, itchy rash	1.31 (0.62–2.79); 0.48	2.07 (0.86–5.00); 0.11	0.37 (0.05–2.76); 0.33	0.60 (0.08–4.63); 0.62	1.45 (0.71–2.96); 0.31	2.26 (0.99–5.17); 0.054
Physician-diagnosed eczema	2.38 (1.07–5.29); 0.03	5.62 (2.09–15.13); 0.001	—§	—§	2.28 (1.03–5.04); 0.04	4.21 (1.63–10.85); 0.003

HR = Hazard ratio; CI = confidence interval; SPT = skin-prick test; IgE = immunoglobulin E.
 *A positive SPT result indicates a net wheal ≥ 3 mm; a positive IgE level indicates ≥ 0.35 kU/L.
 #Adjusted for age, sex, race, smoking status, current asthma, hay fever, number of positive SPT results, and mouse allergen exposure.
 §There were no participants with physician-diagnosed eczema who developed IgE sensitization to mouse, so statistical models could not be run.

Table 3 Associations between chronic, itchy rash vs. physician-diagnosed eczema and incident mouse sensitization; adjusted for self-reported respirator use

Risk Factor	Mouse Sensitization Outcome, HR (95% CI); <i>p</i> Value*					
	Positive SPT Result			Positive IgE Level		
	Crude	Adjusted#	Crude	Adjusted#	Crude	Adjusted#
Chronic itchy rash	1.31 (0.62–2.79); 0.48	1.36 (0.34–5.52); 0.66	0.37 (0.05–2.76); 0.33	—§	1.45 (0.71–2.96); 0.31	0.86 (0.23–3.21); 0.82
Physician-diagnosed eczema	2.38 (1.07–5.29); 0.03	3.90 (0.99–15.4); 0.05	—¶	—¶	2.28 (1.03–5.04); 0.04	2.50 (0.69–9.07); 0.17

HR = Hazard ratio; CI = confidence interval; SPT = skin-prick test; IgE = immunoglobulin E.
 *A positive SPT result indicates a net wheal ≥ 3 mm; a positive IgE level indicates ≥ 0.35 kU/L.
 #Adjusted for age, sex, race, smoking status, current asthma, hay fever, number of positive skin tests, mouse allergen exposure, and self-reported respirator use.
 §The model was no longer able to be run after additional adjustment.
 ¶There were no participants with physician-diagnosed eczema who developed IgE sensitization to mouse, so statistical models could not be run.

Figure 2. Kaplan-Meier plot of time to mouse sensitization, by physician-diagnosed eczema. Solid line = participants without a physician diagnosis of eczema, Dashed line = participants with a physician diagnosis of eczema, p-value shown is for the log-rank test statistic. Mouse sensitization is defined as either a positive skin prick test (net wheal ≥ 3 mm) or mouse-specific IgE test (≥ 0.35 kU/L).

more severe skin barrier dysfunction,¹⁰ which leads to greater risk of developing allergic sensitization.³

Our study had several notable strengths and limitations. The prospective design and repeated, careful assessment of sensitization in a large number of participants were strengths, whereas the modest number of participants with incident sensitization limited our ability to evaluate incident laboratory animal allergy as an outcome. We also were unable to sufficiently study mouse-specific IgE as an outcome because none of the participants with physician-diagnosed eczema went on to develop mouse-specific IgE. Because physician-diagnosed eczema was by self-report and not physician diagnosis, there was potential for misclassification of eczema. However, eczema status was ascertained before the outcome was measured, so that any misclassification of eczema would not be expected to vary by the development of sensitization. In this scenario of nondifferential misclassification, results were biased toward no association rather than toward an association, as we observed here. Finally, these results may

not be generalizable to other populations with eczema because these participants were generally healthy adults employed in mouse production and research facility.

CONCLUSION

Among adult workers at a mouse production and research facility, physician-diagnosed eczema was a risk factor for incident mouse sensitization, independent of multiple measures of atopy. These findings indicated that eczema may be a risk factor for incident animal allergen sensitization throughout life.

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