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Rhinovirus and serum IgE are associated with acute asthma exacerbation severity in children

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To the Editor

More than 80% of asthma exacerbations in children are associated with respiratory viral infections, with human rhinoviruses accounting for up to two-thirds of such episodes.[1] Although it is clear that rhinoviruses are a trigger for asthma exacerbation, the role that rhinovirus infection plays in modulating the acute severity of asthma exacerbation has not been well characterized. Here, we show that rhinovirus-triggered asthma exacerbation is associated with higher acute severity compared with other noninfectious, presumably allergen-triggered causes of asthma exacerbation. We further hypothesized that interactions

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between rhinoviruses and allergen sensitization status contribute to interindividual variation in acute exacerbation severity.

In this observational prospective cohort study, 183 subjects aged 6 to 17 years with physician-diagnosed asthma were enrolled and phenotyped both at the time of acute asthma exacerbation and when they had returned to symptomatic baseline. Nasal swabs were tested for 12 common respiratory viruses by PCR. Summary data on viral infections for all enrolled subjects (n = 183) are presented in Table E1 and study cohort characteristics are presented in Table E2 in this article's Online Repository at www.jacionline.org. *Allergen sensitization* was defined as a specific IgE level of 0.35 kU/L or more. Mouse (*Mus musculus* 1 [Mus m1]) and dust mite (*Dermatophagoides farinae* 1 [Der f1]) levels in settled dust from subject's bedrooms were measured (see this article's Methods section in the Online Repository at www.jacionline.org). Allergen exposure cutoffs were 0.5 μg/g for Mus m1 and 2 μg/g for Der f1. The Acute Severity Score is a composite score combining the Modified Pulmonary Index Score[2] (a validated indicator of severity of illness in children with asthma) combined with the duration over which beta-agonist therapy was weaned (see this article's Methods section). As such, this score conveys information about both initial illness severity and duration of treatment.

Comparisons were made between subjects who were single positive for rhinovirus infection and those subjects who were negative for all viruses in the respiratory viral panel (referred to as virus negative). Subjects who were positive for multiple viruses were excluded. Univariate and multivariate linear regression were used to investigate the association between the Acute Severity Score and predictor variables.

We found that subjects with rhinovirus infection (n = 95) had Acute Severity Scores that were significantly more severe than those of subjects who were virus negative (n = 60; Fig 1, A; see Table E3 in this article's Online Repository at www.jacionline.org), even after adjusting for common risk factors associated with asthma severity. We also examined multiple other types of outcome variables, and in each case, rhinovirus infection was associated with significantly worse acute severity (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org). Hence, the association between rhinovirus and acute asthma exacerbation severity is robust to the outcome measure used.

We next looked for factors that might contribute to interindividual differences in acute asthma exacerbation severity, focusing on allergen sensitization because rhinoviruses are more likely to trigger asthma exacerbation in allergic children.[3] We found that baseline mouse-specific IgE and baseline dust mite–specific IgE levels each interact with rhinovirus infection to alter severity: rhinovirus-triggered asthma exacerbation became more severe as the degree of allergen sensitization increased (Fig 1, B and C). Together, the combination of rhinovirus infection and allergen sensitization explains up to 56% of the variation in the Acute Severity Score.

Allergen-specific IgE levels are in part determined by exposure to the corresponding allergen,[4] raising the possibility that an environment: environment interaction between allergen exposure and rhinovirus infection influences asthma exacerbation severity. We

investigated this possibility by looking for an interaction between asthma severity, bedroom allergen exposure, and allergen-specific IgE levels (see Fig E1 in this article's Online Repository at www.jacionline.org). First, we found that there was a significant interaction between bedroom allergen exposure and allergen-specific IgE levels that influenced baseline asthma symptoms in sensitized subjects (Fig E1, A and B). However, the same type of interaction does not influence acute exacerbation severity (Fig 1, C and D).

We next compared IgE levels at the time of acute asthma exacerbation to levels when subjects were at their symptomatic baseline. We observed that at the time of asthma exacerbation, subjects who were rhinovirus positive demonstrated an increase compared with baseline in mouse-specific IgE levels, dust mite–specific IgE levels, and total IgE levels that were all significantly greater than the increases observed in virus-negative subjects (Fig 2, A-C). This increase in serum IgE remained significant after adjusting for factors known to influence IgE levels.

We then investigated how this increase in IgE at the time of rhinovirus-triggered asthma exacerbation related to acute asthma severity. We found that for both mouse-specific and dust mite–specific IgE, rhinovirus-triggered asthma exacerbation becomes more severe as the magnitude of the rise in allergen-specific IgE levels increases (Fig 2, D and E), even after adjusting for common risk factors associated with asthma severity. In contrast, we did not observe a significant interaction between the acute increase in total IgE and acute exacerbation severity (Fig 2, F). Notably, if the analyses in Figures 1 and 2 are restricted to sensitized subjects only, the associations remain significant (data not shown). Furthermore, the interactions between rhinovirus and allergen sensitization shown in Figures 1 and 2 are reproducible using any of the continuous outcome measures in Table E4 (data not shown).

In one of the largest reported cohorts examining rhinovirus infection and pediatric asthma, we found that rhinovirus infection is not simply a trigger for pediatric asthma exacerbation but is also robustly associated with episodes of acute asthma exacerbation that are significantly more severe that those caused by noninfectious, presumably allergic triggers. We also found that mouse and dust mite sensitization strongly contribute to interindividual variation in the acute severity of rhinovirus-triggered asthma exacerbation. In addition, mouse-specific and dust mite–specific IgE levels both rise during rhinovirus infection, and the magnitude of this rise is strongly and specifically associated with the severity of rhinovirus-triggered asthma exacerbation. Collectively, our results demonstrate that a substantial portion of the interindividual variation in acute asthma exacerbation severity is attributable to the combination of rhinovirus infection and factors that regulate allergen sensitization, and IgE might play a causal role in modifying acute severity. This study fills an important gap in the understanding of risk factors that are associated with the severity of pediatric acute asthma exacerbation.[6]

Our results examining the effect of environmental allergen exposure and acute exacerbation severity suggest the following: (1) the degree of allergen sensitization is more closely associated with acute asthma exacerbation severity than is the degree of recent exposure to allergens, and (2) factors other than recent environmental allergen exposures may also influence allergen-specific IgE levels. Because genetic background is known to contribute to

variation in both total IgE and allergen-specific IgE levels,[7,8] one intriguing possibility is that interindividual differences in the severity of acute asthma exacerbation observed here are influenced by gene:environment interactions between genetic variants that influence IgE levels and environmental exposure to rhinovirus infection.

This study has several limitations. First, this is an observational study and does not establish causality. Second, allergen levels often were not measured in temporal proximity to episodes of asthma exacerbation. Third, a single dust measurement may be a poor reflection of an individual's total allergen exposure history. Fourth, in this study we establish the validity of the Acute Severity Score only for those patients presenting to the emergency department with asthma exacerbation. The general applicability of this measure to other populations would need to be established with additional prospective studies. Finally, the associations that we identified in a cohort of children presenting to the emergency department with asthma exacerbation may not be generally applicable to other populations of children with asthma.

In summary, we show an association between rhinovirus infection and acute asthma exacerbation severity in children, and demonstrate interactions between rhinovirus infection and allergen-specific IgE levels that help to explain additional interindividual variation in disease manifestation. Our results suggest the possibility that therapies targeting IgE-initiated signaling events, which have been shown to ameliorate chronic asthma symptoms,[9] may also be effective in reducing the severity of acute asthma exacerbation. Last, our results suggest the possibility that joint effects of genetic and environmental factors might influence rhinovirus-triggered asthma exacerbation severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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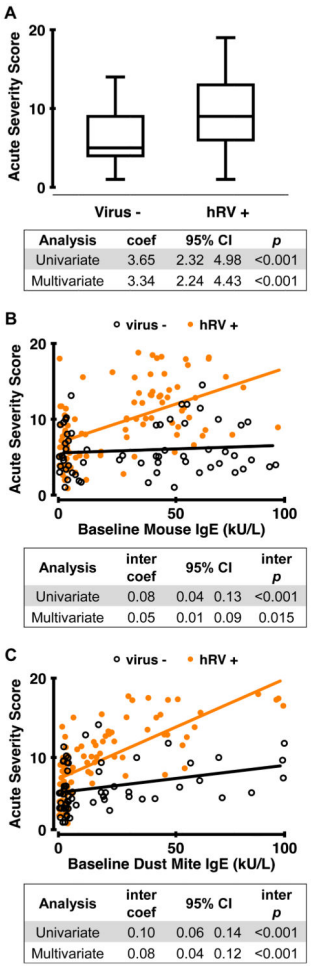


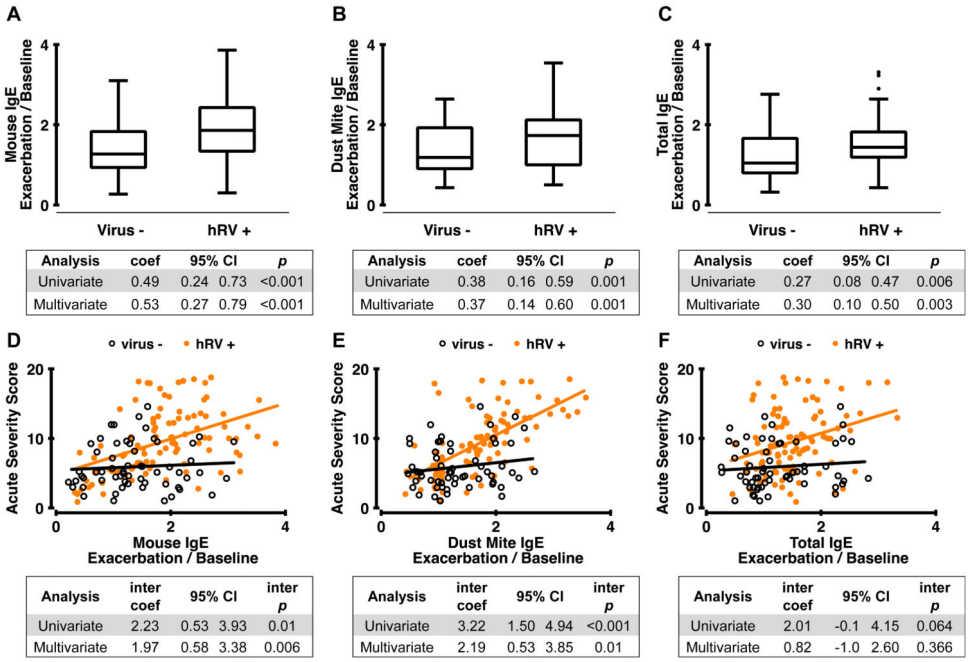
Analysis	coef	95% CI		p
Univariate	3.65	2.32	4.98	<0.001
Multivariate	3.34	2.24	4.43	<0.001

Analysis	inter coef	95% CI		inter p
Univariate	0.08	0.04	0.13	<0.001
Multivariate	0.05	0.01	0.09	0.015

Analysis	inter coef	95% CI		inter p
Univariate	0.10	0.06	0.14	<0.001
Multivariate	0.08	0.04	0.12	<0.001

Fig 1.

Rhinovirus infection interacts with mouse-specific and dust mite–specific IgE levels in relation to acute asthma exacerbation severity. **A**, Rhinovirus-positive subjects (hRV+, n = 95) demonstrate higher acute severity than do virus-negative subjects (virus –, n = 60). The linear regression coefficient, 95% CI, and *P* value are shown (multivariate analysis adjusted for age, sex, race, annual income, lung function, baseline asthma severity, symptom duration, medication adherence, total number of ImmunoCAP positives, and season). Rhinovirus infection interacts with both baseline mouse-specific (**B**) and dust mite–specific IgE (**C**) levels. For panels (*B*) and (*C*), the linear regression coefficients, 95% CIs, and *P* values for the interaction between rhinovirus status and the respective allergen-specific IgE levels are shown. *coef*, Coefficient.



Analysis	coef	95% CI		p
Univariate	0.49	0.24	0.73	<0.001
Multivariate	0.53	0.27	0.79	<0.001

Analysis	coef	95% CI		p
Univariate	0.38	0.16	0.59	0.001
Multivariate	0.37	0.14	0.60	0.001

Analysis	coef	95% CI		p
Univariate	0.27	0.08	0.47	0.006
Multivariate	0.30	0.10	0.50	0.003

Analysis	inter coef	95% CI		inter p
Univariate	2.23	0.53	3.93	0.01
Multivariate	1.97	0.58	3.38	0.006

Analysis	inter coef	95% CI		inter p
Univariate	3.22	1.50	4.94	<0.001
Multivariate	2.19	0.53	3.85	0.01

Analysis	inter coef	95% CI		inter p
Univariate	2.01	-0.1	4.15	0.064
Multivariate	0.82	-1.0	2.60	0.366

Fig 2.

Rhinovirus infection is associated with an acute rise in IgE levels. Rhinovirus (hRV+, n = 95) is associated with an acute increase in mouse-specific (**A**), dust mite–specific (**B**), and total IgE (**C**) levels compared with virus-negative subjects (virus–, n = 60). IgE levels are expressed as the fold-change of exacerbation levels over baseline levels. For panels (*A*), (*B*), and (*C*), linear regression coefficients, 95% CIs, and *P* values are shown (multivariate analysis adjusted for age, sex, race, season, and time between measurement of exacerbation and baseline IgE levels). Rhinovirus interacts with the fold-change in both mouse-specific (**D**), and dust mite–specific IgE (**E**) levels in terms of acute asthma severity, but not with total IgE level (**F**). For panels (*D*), (*E*), and (*F*), the linear regression coefficients, 95% CIs, and *P* values for the interaction between rhinovirus status and fold-change in IgE levels are shown (multivariate analyses adjusted for age, sex, race, annual income, lung function, baseline asthma severity, symptom duration, medication adherence, total number of ImmunoCAP positives, and season). *coef*, Coefficient.

Table I

Characteristics of study cohort

Characteristic	Total	Virus–	hRV+	*P* value
Enrolled, n (% total)	155 (100)	60 (38.7)	95 (61.3)	NA
Age (y), mean ± SD	9.9 ± 3.2	10.3 ± 3.1	9.7 ± 3.2	.321
Male, n (%)	103 (66.5)	42 (70)	61 (64.2)	.489
Eosinophils (10^3 cells/μL), mean ± SD	0.43 ± 0.47	0.42 ± 0.38	0.43 ± 0.53	.915
Ethnicity, n (%)				
Black/African	75 (48.4)	28 (46.7)	47 (49.5)	.745
Hispanic	35 (22.6)	16 (26.7)	19 (20.0)	.43
White/European	35 (22.5)	13 (21.6)	22 (23.1)	.43
Other	10 (6.5)	3 (5.0)	7 (7.4)	.742

NA, Not available/applicable.