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Assessment of humoral and cell-mediated immune response to measles–mumps–rubella vaccine viruses among patients with asthma

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Abstract

Little is known about the influence of asthma status on humoral and cell-mediated immune responses to measles–mumps–rubella (MMR) vaccine viruses. We compared the virus-specific IgG levels and lymphoproliferative response of peripheral blood mononuclear cells to MMR vaccine viruses between asthmatic and nonasthmatic patients. The study subjects included 342 healthy children aged 12–18 years who had received two doses of the MMR vaccine. We ascertained asthma status by applying predetermined criteria. Of the 342 subjects, 230 were available for this study of whom 25 were definite asthmatic patients (10.9%) and the rest of subjects were nonasthmatic patients. The mean of the log-transformed lymphoproliferative responses between definite asthma and nonasthma who had a family history of asthma were for measles, 0.92 ± 0.31 versus 1.54 ± 0.17 ($p = 0.125$); for mumps, 0.98 ± 0.64 versus 2.20 ± 0.21 ($p = 0.035$); and for rubella, 0.12 ± 0.37 versus 0.97 ± 0.16 ($p = 0.008$), respectively, adjusting for the duration between the first MMR vaccination and determination of the immune responses. There were no such differences among children without a family history of asthma. MMR virus–specific IgG levels were not different between study subjects with or without asthma. The study findings suggest asthmatic patients may have a suboptimal cell-mediated immune response to MMR vaccine viruses and a family history of asthma modifies this effect.

Despite the introduction of widespread measles–mumps–rubella (MMR) immunization programs, mumps, measles, and rubella continue to cause outbreaks throughout the world. In the United States, sporadic epidemics of measles, mumps, and rubella continue to occur despite the fact that most of these subjects have received one or two doses of MMR vaccine.[1,2] For example, the largest mumps outbreak in 20 years took place in the United States in 2006.[3] A total of 6584 cases were reported in 2006 but there was no mortality related to this outbreak. This mumps outbreak raises a significant public health concern because it occurred despite high MMR vaccine coverage. The national coverage of one-dose mumps vaccination among preschoolers was 89% or more nationwide and 86% or more in highly affected states. In 2006, the national two-dose coverage among adolescents, who

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were the highest risk group during the mumps outbreak, was 87%, the highest in U.S. history.[3]

According to the data from the National Health and Nutrition Examination Survey conducted during 1999–2004, the overall seroprevalence of measles IgG antibody, was 95.9% so measles seropositivity was at or above the estimated threshold of 93–95% that is needed for elimination of measles and the ongoing transmission of measles virus was declared to be eliminated in the United States in 2000. Although, the MMR vaccine is efficacious (~90%),[4] the rate of vaccine failure or loss of immunity after one or two doses of MMR vaccines is not trivial.[5,6] In addition, there is significant variation of measles virus–specific IgG levels among different ethnic groups and birth cohorts.[7–9]

At present, it is not known why the MMR epidemic suddenly occurred and resulted in extraordinary mortality and morbidity even among populations who were considered to be properly vaccinated[1,2,10] despite no altered biological characteristics of virus. Thus, it is likely that host factors play a role in humoral and cell-mediated immunity (CMI) responses in long-term protection against viral infections. In this respect, asthma has significantly increased over the past 20 years in developed countries including the United States[11] and asthma is the most common chronic disease among childhood and causes major morbidity in adults affecting 32 million Americans and 300 million people worldwide.[12] Importantly, asthma has been reported to be associated with poor humoral and/or CMI responses to various vaccines.[13–15] The impact of asthma on susceptibility to microbial infections at a population level is not known, but two independent studies reported the most common chronic condition among individuals who were admitted to the hospital or intensive care units with the novel H1N1 influenza virus was asthma, suggesting a potential role of asthma in determining susceptibility to or severity of viral infections.[16,17]

At present, the humoral and CMI responses to MMR vaccine viruses in individuals with asthma have not been investigated. The results of this investigation are likely to give us an insight into the role of asthma in MMR immunity and potentially immunity to other viral infections. We conducted a cross-sectional study to compare the MMR virus–specific IgG levels and lymphoproliferative response of peripheral blood mononuclear cells (PBMCs) to MMR vaccine viruses between children with asthma and those without asthma.

METHODS

Study Setting

With the exception of a higher proportion of the working population employed in the health care industry, characteristics of the city of Rochester and Olmsted County populations are similar to those of the U.S. white population.[5,18] Because the Rochester Epidemiology Project links records to all residents in the county, all inpatient and outpatient medical records are available for this study, allowing for verification of vaccine status and ascertainment of asthma through comprehensive medical record reviews. Therefore, Olmsted County, MN, is an excellent study setting to conduct this current study because medical care is virtually self-contained within the community with a unified medical record system for research among two medical centers for the past 90 years.

Study Subjects and Design

The study protocol was approved by the institutional review boards at both the Mayo Clinic and the Olmsted Medical Center. The study was a cross-sectional study. The study subjects of the original study were described in a previous article[19] and 342 subjects from the original study were eligible for this present study. The MMR vaccination is part of a routine program and all enrolled participants had documentation in their medical record of having

received two doses of MMR-II vaccine. All enrolled participants resided in Olmsted County, MN, where no wild-type MMR virus had circulated in the area throughout the subjects' lifetime. We excluded subjects who did not grant research authorization for medical record review.

MMR Vaccine Virus-Specific IgG Levels

The details of the assay method were reported previously.[20] Quantitative levels of measles, mumps, and rubella IgG antibody titers for all serum specimens were determined by the Enzygnost (Dade Behring, Marburg, Germany) antimeasles virus/IgG enzyme immunoassay (EIA; sensitivity, 99.6%; specificity, 100%), antimumps virus/IgG EIA (sensitivity, 95.4%; specificity, 93.7%), and antirubella virus/IgG EIA (sensitivity, 100%; specificity, 98.5%), respectively, according to the manufacturer's instructions. The coefficients of variation in our laboratory for the measles, mumps, and rubella assays were 3.8, 4.1, and 4.0%, respectively.

Lymphoproliferative Response of PBMCs to MMR Viruses

The details of the assay method were reported previously.[21] Briefly, MMR-specific T-cell responses were measured by proliferation of fresh PBMCs (2×10^5 cells/well) incubated in RPMI-1640 medium, supplemented with 5% autologous sera with live attenuated individual MMR vaccine virus (Wistar RA 27/3 strain, 75 pfu/well) and compared with unstimulated cell control wells. T-lymphocyte proliferation was measured after 4 days by [^{3}H]-tritiated thymidine uptake. Cells were pulsed with 1 μCi of tritiated thymidine (Perkin-Elmer, Boston, MA) for 18 hours and then harvested onto glass fiber filters, using a 96-well harvesting system (Skatron Instruments, Lier, Norway). For each subject, median cpm were calculated for unstimulated cells, as well as for cells stimulated with MMR vaccine virus. Results were then expressed as antigen-specific stimulation indices.

Determination of Asthma

The criteria for asthma were developed by a previous study and a number of publications on asthma epidemiology research have used these criteria to define asthma.[22–24] These criteria are detailed in Table 1. Data abstractors were completely blinded to data on immune responses to the MMR vaccine virus and observation bias or detection bias was unlikely. The date of onset of asthma (incident date) was defined as the earliest constellation of symptoms found in the medical record that met the predetermined criteria for asthma in Table 1 regardless of the physician diagnosis of asthma. In this study, we included only children who met the criteria for definite asthma and nonasthmatic children at the time of enrollment of the original study.

Other Variables

We also assessed the association between immune responses to MMR vaccine viruses and other potential covariates including sociodemographic variables and the family history of asthma. The family history of asthma was defined by the presence of asthma among first-degree relatives.

Statistical Analysis

The dependent variables were MMR vaccine virus-specific IgG levels and PBMC lymphoproliferative response to MMR vaccine viruses. PBMC lymphoproliferative responses were log transformed for analysis because it had a skewed distribution. The main independent variable was asthma status and other covariates of interest included sociodemographic characteristics and asthma-related variables such as family history of asthma. To determine the association between immune responses to MMR vaccine viruses

and asthma status and other covariates, we used an analysis of covariance (ANCOVA) controlling for duration between the first MMR vaccination and determination of the immune responses.

RESULTS

Study Cohort

Of the 342 original subjects, 19 were not eligible for this study because their parents did not provide research authorization for medical record review. Of the 323 eligible subjects, one subject did not have laboratory data, and 92 children did not meet the criteria for definite asthma at the time of enrollment of the original study. Thus, 230 subjects were available for this study of whom 25 were definite asthmatic patients (10.9%) and the rest of the subjects were nonasthmatic patients. The sociodemographic and clinical characteristics of the eligible subjects for this study and the excluded subjects are summarized in Table 2. The results suggested no significant differences in characteristics between included and excluded subjects. The mean age of asthmatic patients at the index date of asthma was 5 years.

The Relationship between Lymphoproliferative Responses to MMR Vaccine Virus and Asthma Status

The results for the comparison of the log-transformed lymphoproliferative response to MMR vaccine viruses for nonasthma and definite asthma are summarized in Table 3. Children with asthma had a tendency toward poorer lymphoproliferative immune responses to MMR vaccine viruses, particularly the rubella vaccine virus, compared with nonasthmatic children, adjusting for the duration between the first MMR vaccination and determination of immune responses. To assess the potential immunogenetic influence, we also assessed the influence of family history of asthma on PBMC lymphoproliferative responses and the results are summarized in Table 3. Overall, children with a family history of asthma had poorer PBMC lymphoproliferative responses to MMR vaccine viruses, particularly to the rubella and measles vaccine viruses. To assess the potential interaction between asthma status and family history of asthma in PBMC lymphoproliferative responses, we assessed the relationship between PBMC lymphoproliferative response and asthma status, which was stratified by a family history of asthma. The results are summarized in Table 4. Although asthmatic patients with a family history of asthma had poorer PBMC responses to MMR vaccine viruses than nonasthmatic patients, asthmatic patients without a family history of asthma had similar PBMC responses to nonasthmatic patients, suggesting effect modification for the impact of asthma status on PBMC responses to MMR vaccine viruses by a family history of asthma. None of the sociodemographic factors examined including gender, ethnicity, age at enrollment in the study, and maternal educational levels were significantly associated with PBMC lymphoproliferative responses to MMR vaccine viruses (data not shown).

The Relationship between the MMR Vaccine Virus-Specific IgG Levels and Asthma Status

The results of MMR vaccine virus-specific IgG levels between children with and without asthma as well as those with or without family history of asthma are summarized in Table 5. Although there were trends toward lower measles and mumps-specific IgG levels in asthmatic patients, the differences were not statistically significant. Similarly, no significant differences in MMR vaccine virus-specific IgG levels between children with and without a family history of asthma were apparent. Other variables such as age, ethnicity, and maternal educational were not significantly associated with MMR vaccine virus-specific IgG levels (data not shown). However, male patients had lower levels of rubella virus–specific IgG (mean ± SE: 6.20 ± 0.27) than female patients (7.04 ± 0.26; $p = 0.018$), and this was true for

mumps virus–specific IgG levels (26.88± versus 32.05 ± 1.29, respectively; $p < 0.001$) as well.

DISCUSSION

Although humoral immunity is critical for long-term protection against viral infections, not all seronegative individuals who have primary or secondary vaccine failure develop viral disease on exposure to an index case. Patients with abnormal cellular immunity (*e.g.*, leukemia or human immunodeficiency virus), who have a protective antibody level against a viral vaccine (*e.g.*, measles), have been reported to develop infections and high mortality from viral infection,[10,25] suggesting the importance of CMI against viral infection. In addition, because temporal waning of antirubella antibody (–2.4%/year) has been reported,[26] without a booster vaccination individuals may eventually be susceptible to rubella. This further highlights the significance of CMI for long-term protection and the importance of investigating the influence of host factor on immune response to viral antigens.

In this respect, our study results indicate that asthmatic children and adolescents with a family history of asthma had much poorer lymphoproliferative responses (a measure for CMI) to rubella and mumps vaccine viruses, compared with those without asthma (see Table 4). Although lymphoproliferative responses to measles vaccine virus in asthmatic patients were poorer than that in nonasthmatic patients, the difference only approached statistical significance. These results took into account the duration between MMR vaccination and determination of immune responses. In our study cohort, only one subject was on inhaled corticosteroids within 30 days before the determination of the immune response and, thus, these findings are unlikely to be explained by the influence of corticosteroids, although corticosteroid has not been associated with poorer humoral or cell-mediated responses (CMI) to vaccines.[17,27,28]

None of the subjects had any history of immunodeficiency disorder. Other potential factors such as gender and race did not affect CMI to MMR vaccine viruses. Furthermore, because normal responses to a nonspecific antigen such as phytohemagglutinin (used as a positive control for lymphoproliferative assay) were observed in all study subjects (data not shown), the lower T-cell response to virus might be caused by a lower number of virus-specific T cells (*i.e.*, cognate T-cell repertoire against MMR vaccine viruses) and not to a reduced proliferative capacity of T cells to MMR vaccine virus in patients with asthma. Thus, it can be postulated that CMI (and T-cell memory) may wane more rapidly over time among asthmatic patients with a family history of asthma, compared with nonasthmatic patients, although they had normal humoral immune responses to MMR vaccine viruses as shown in our study. However, this more rapid waning of CMI among asthmatic patients with a family history of asthma may result in a significant impact on both humoral and CMI against measles, mumps, and rubella virus infections over time. For example, a study reported that a significant proportion of asthmatic patients aged 1.6–17 years, who had received two doses of MMR vaccine, became seronegative for measles (40–43%) and mumps (25–39%) immunity.[15] These data may suggest that asthmatic patients may lose immunity more rapidly and become a susceptible population for outbreaks of serious infectious diseases and, thus, there may be a potential conjunction to asthma prevalence and the 2006 outbreak of mumps in the United States. Suboptimal CMI response to other vaccines has been reported among individuals with asthma or atopic dermatitis.[29,30] For example, a previous study reported that 9.2% (8/87) of asthmatic children and adults and 1.2% (1/86) of normal individuals failed to mount a delayed-type hypersensitivity response to tetanus toxoid ($p < 0.02$).[14] Similarly, 45% of patients with atopic dermatitis and 27% of normal individuals failed to mount a delayed-type hypersensitivity response ($p < 0.001$).[29] Therefore, based on our study results and the literature, asthmatic patients, particularly those with a family

history of asthma who have suboptimal CMI against measles, mumps, and rubella viruses might be at an increased risk of developing viral disease on exposure to virus, compared with those without asthma. The potential impact of asthma status and family history of asthma on risk of measles, mumps, and rubella viral infection at a population level needs to be investigated.

Importantly, the impact of asthma status on PBMC lymphoproliferative response to MMR vaccine viruses depends on family history of asthma (*i.e.*, there was a poorer CMI responses to MMR vaccine). These data suggest that a family history of asthma may be an important effect modifier for the impact of asthma status on CMI against MMR vaccine viruses and such an impact may be mediated through immunogenetic mechanisms. We postulate that a family history of asthma may be a genetic marker for HLA DR3 gene and the effect modification by a family history of asthma may be mediated through HLA DR3 gene given the known poor immune response to measles vaccine response among HLA DR3 gene carriers.[4]

The strength of this study was that the self-contained health care environment and unified medical record system for research allowed us to ascertain asthma status reliably. Our study has the inherent limitations of being a retrospective study for outcome measures and asthma ascertainment. However, the dependent variables are objective laboratory values so detection bias was unlikely and a previous study documented the high degree of reliability of our asthma criteria.[24] In this study, we did not include children who did not meet the criteria for definite asthma such as probable asthma. However, subjects who were excluded and those included were similar with regard to sociodemographic and clinical characteristics. Our study subjects were predominantly white children so the results might not be applicable to those with other ethnic backgrounds. Finally, our study is based on a small sample size, especially asthmatic subjects, which is subject to replication of the findings in a study with a larger sample size.

In conclusion, asthmatic patients had a suboptimal CMI response to MMR vaccine viruses but a family history of asthma modifies this effect. Given the temporal waning of antibody against vaccination over time and the important role of CMI against viral infections, asthmatic patients may be at an increased risk of developing viral infection over time. The immunogenetic mechanisms for poor CMI responses to MMR vaccine viruses in asthmatic patients need to be determined.

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Table 1

The criteria for asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma plus any one of the following three conditions were present OR if each of the following three conditions were present, and they were considered to have *probable* asthma if the first two of the following three conditions were present:	
1.	History of cough, dyspnea, and/or wheezing, OR history of cough and/or dyspnea plus wheezing on examination.
2.	Substantial variability of symptoms from time to time or periods of weeks or more when symptoms were absent. AND
3.	Two or more of the following:
	Sleep disturbance by nocturnal cough and wheeze
	Nonsmoker (≥14 yr of age)
	Nasal polyps
	Blood eosinophilia of >300/μL
	Positive wheal and flare skin tests or elevated serum IgE
	History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen
	Pulmonary function tests showing one FEV_1,or FVC of <70% predicted and another with at least 20% improvement to an FEV_1 of >70% predicted or a methacholine challenge test showing ≥20% fall in FEV_1
	Favorable clinical response to bronchodilator

FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

Table 2

Sociodemographic and clinical characteristics of the study subjects and those who were excluded from the study

	Included Subjects (*n* = 230)	Excluded Subjects (*n* = 92)	*p* Value
Gender (male, %)	51	59	0.20
Ethnicity (%)			
White	99	98	0.57
Nonwhite	1	2	
Age at enrollment, yr (mean ± SD)	16.1 ± 1.94	16.1 ± 2.00	0.75
Maternal educational levels (%)			
High school graduate	15	18	0.59
Some college education	43	41	
College graduate	26	32	
Graduate school education	15	9	
Family history of asthma (%)			
Yes	23	30	0.20
No	77	70	
Duration between MMR vaccination and enrollment, yr (mean ± SD)	15.0 ± 2.0	14.9 ± 1.95	0.84

MMR = mumps-measles-rubella.

Table 3

Comparisons of the log-transformed peripheral blood mononuclear cell (PBMC) lymphoproliferative response to measles-mumps-rubella (MMR) vaccine viruses between children with and without asthma as well as those with or without family history of asthma

		p Value*
PBMC lymphoproliferative response to measles vaccine virus (mean ± SE)		
Asthma status		
Yes	1.59 ± 0.24	0.189
No	1.86 ± 0.08	
Family history of asthma		
Yes	1.42 ± 0.16	0.010
No	1.94 ± 0.10	
PBMC lymphoproliferative response to mumps vaccine virus (mean ± SE)		
Asthma status		
Yes	1.88 ± 0.33	0.176
No	2.26 ± 0.09	
Family history of asthma		
Yes	1.98 ± 0.22	0.171
No	2.30 ± 0.11	
PBMC lymphoproliferative response to rubella vaccine virus (mean ± SE)		
Asthma status		
Yes	0.77 ± 0.20	0.041
No	1.20 ± 0.07	
Family history of asthma		
Yes	0.78 ± 0.16	0.009
No	1.26 ± 0.10	

* The p values analysis of covariance adjusting for duration between MMR vaccination and enrollment in the study (specimen collection).

Table 4

Comparisons of the log-transformed peripheral blood mononuclear cell (PBMC) lymphoproliferative response to measles-mumps-rubella (MMR) vaccine viruses between subjects with and without asthma stratified by the family history of asthma

Presence of Family History of Asthma (*n* = 44)			Absence of Family History of Asthma (*n* = 146)		
Asthmatic Patients (*n* = 8)	**Nonasthmatic Patients (*n* = 36)**	***p*-Value**	**Asthmatic Patients (*n* = 14)**	**Nonasthmatic Patients (*n* = 132)**	***p* Value**
PBMC lymphoproliferative response to measles vaccine virus (mean ± SE)					
0.92 ± 0.31	1.54 ± 0.17	0.125	1.94 ± 0.35	1.94 ± 0.10	0.929
PBMC lymphoproliferative response to mumps vaccine virus (mean ± SE)					
0.98 ± 0.64	2.20 ± 0.21	0.035	2.35 ± 0.39	2.29 ± 0.11	0.971
PBMC lymphoproliferative response to rubella vaccine virus (mean ± SE)					
0.12 ± 0.37	0.97 ± 0.16	0.008	1.32 ± 0.19	1.26 ± 0.10	0.795

Negative value in mean indicates the value below zero because the results were log transformed; all p values were based on analysis of covariance adjusting for duration between MMR vaccination and enrollment in the study (i.e., collection of specimen).

Table 5

Comparisons of measles-mumps-rubella (MMR) vaccine virus-specific IgG levels between children with and without asthma as well as those with or without family history of asthma

		p Value*
Measles vaccine virus-specific IgG levels (mean ± SE)		
Asthma status		
Yes	1.59 ± 0.24	0.307
No	1.86 ± 0.08	
Family history of asthma		
Yes	37.50 ± 2.71	0.153
No	42.32 ± 1.56	
Mumps vaccine virus-specific IgG levels (mean ± SE)		
Asthma status		
Yes	25.89 ± 1.85	0.169
No	29.83 ± 0.86	
Family history of asthma		
Yes	29.36 ± 2.24	0.919
No	29.07 ± 0.88	
Rubella vaccine virus-specific IgG levels (mean ± SE)		
Asthma status		
Yes	6.67 ± 0.20	0.502
No	6.16 ± 0.48	
Family history of asthma		
Yes	7.00 ± 0.48	0.281
No	6.48 ± 0.22	

*The p values analysis of covariance adjusting for duration between MMR vaccination and enrollment in the study (specimen collection).