

Varicella Zoster Virus (Wild-Type) Infection, but not Varicella Vaccine, in Late Childhood Is Associated With Delayed Asthma Onset, Milder Symptoms, and Decreased Atopy

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Varicella zoster virus (VZV) infection, early in life, has been shown to have a protective role against the development of asthma and atopy in children. It is unknown whether VZV infection in late childhood and adolescence also has an asthma protective effect. We studied whether VZV infection in late childhood and adolescence, or administration of the live attenuated varicella vaccine, provides a similar protective effect. In the present study, we use a retrospective chart review of a pediatric practice ($N = 62$) to analyze the effect of wild-type (WT) VZV infection or recombinant varicella vaccine in children (age 3–21 years) diagnosed with asthma. We found (1) asthma onset occurred 9.4 ± 4.4 years after WT VZV infection (4.4 ± 2.2) by age 13.9 ± 6.5 years, but only 3.0 ± 1.7 years after recombinant vaccine (3.2 ± 3.0 years) at age 5.0 ± 3.6 years ($P = 0.05$); (2) asthma classifications were 61.5% intermittent, 15.4% mild persistent, and 23.1% moderate persistent after WT VZV infection, but were 30.0% intermittent, 36.7% mild persistent, and 33.3% moderate persistent after recombinant vaccine ($\alpha = 0.01$); (3) severe asthma flare-ups requiring inhaled or oral corticosteroids either ≤ 1 year or > 1 year after infection occurred in 0.0% and 30.8% patients after WT infection, and 21.4% and 48.3% after recombinant vaccine ($\alpha = 0.01$); and (4) history of allergies, necessity for allergy referral, and elevated serum IgE levels occurred in 15.4%, 7.7%, and 15.4% of patients who had WT VZV infection before asthma onset, and 36.7%, 33.3%, and 26.7% of patients who received recombinant vaccine ($\alpha = 0.01$). These studies demonstrate that a single episode of varicella infection, even in late childhood and adolescence, is sufficient to delay the onset of asthma symptoms and decrease asthmatic symptoms and flare-ups.

Introduction

IT IS WELL KNOWN that viral infections may influence the development of atopy.^{1,2} It has been suggested, that viral infectious diseases, such as rhinitis or Epstein-Barr virus, during early childhood may have a protective role against the development of asthma and allergy.^{3,4} This appears to be part of the broader “hygiene hypothesis,” which first demonstrated that improved hygiene was associated with increased hay fever, allergic rhinitis and eczema.⁵ Subsequently, a number of studies have explained the “hygiene hypothesis” based on the observations that Th1 responses induced by microbial stimulation can counterbalance allergen-induced Th2 responses.^{6–8}

Studies of Illi et al.⁹ showed that repeated viral infections with rhinovirus or herpes type viruses were inversely

related to developing asthma in early childhood. In particular, infection with varicella zoster virus (VZV) resulting in chickenpox, was shown to be inversely related to developing asthma in early childhood.⁹ However, VZV infection has also been shown to be associated with exacerbation of asthma.¹⁰ It remains unknown whether the VZV infection must occur before the onset of asthma to have a protective effect. Moreover, it is unknown whether administration of the live attenuated varicella vaccine provides a similar protective effect. Previous studies in our laboratory have reported the presence of IgE anti-VZV antibodies after shingles infection; 5 months after shingles infection, serum IgE levels were decreased ($> 30\%$).¹¹

In the present study, we use a retrospective chart review of a pediatric practice to analyze the effect of wild-type (WT)

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VZV infection or recombinant varicella vaccine in children diagnosed with asthma. The results of this study suggest that VZV infection (before diagnosis of asthma) is associated with a delayed asthma onset, milder asthma classifications, and fewer severe asthma flare-ups. None of these protective effects were associated with the varicella vaccine. These findings suggest that VZV infection, even in late childhood and adolescence, has an asthma protective effect.

Materials and Methods

Subjects

Patients ($N = 62$) (m/f, ages 3–21 y/o) from an outpatient pediatric practice in Brooklyn, New York were randomly selected to participate in the study based on the International Classification of Diseases, Ninth Revision (ICD9) diagnosis of asthma (493), between the years 1999 and 2007. Exclusion criteria were refusal to participate, loss to follow-up, and incomplete documentation. Patient history, medications, referrals, and laboratory values were collected from the onsite electronic charting system.

At each visit, parents filled out a questionnaire about their child's general development, including the appearance of asthmatic and allergic symptoms. In particular, parents were asked about symptoms of the skin (pruritus, flushing, urticaria/angioedema), eyes (conjunctival injection, lacrimation, periorbital edema, pruritus), nose/oropharynx (sneezing, rhinorrhea, nasal congestion, metallic taste), upper airway (hoarseness, stridor, sense of choking, laryngeal edema), lower airway (dyspnea, tachypnea, wheezing, cough, cyanosis), and gastrointestinal (nausea/vomiting, abdominal cramping, bloating, diarrhea) after exposure to environmental and dietary triggers. Children with severe allergies and/or unknown allergic triggers were referred to an allergist for further workup with skin prick testing and serology (serum IgE levels).

Asthma classification

Symptom frequency (daytime, nighttime, and exertional) was used for initial classification of asthma severity according to the 1997 National Asthma Education and Prevention Program Expert Panel Report 2 (NAEPP/EPR2) on asthma diagnosis and treatment guidelines.¹²

After initial therapeutic trial, patients were reassessed by the pediatrician at 2–6 weeks and then on an ongoing basis at 1–6-month intervals. If the child's asthma was not well controlled, the asthma severity was upgraded and the therapeutic regimen was advanced using a stepwise treatment approach as suggested in the NAEPP/EPR2 Guidelines. For inhaled corticosteroid (ICS) use, the average daily microgram dose actually taken was classified as low, medium, or high based on the NAEPP/EPR2 Guidelines. Leukotriene receptor antagonists use was considered if short-acting β -agonist therapy was taken on 5 or more of the preceding 7 days.

Intermittent asthma included patients receiving only short-acting β -agonist as needed. Mild persistent asthma included patients receiving either low-dose ICS (preferred) or alternative controller medication (leukotriene receptor antagonists, cromolyn, nedocromil, or theophylline). Moderate persistent asthma included patients receiving either medium-dose of an ICS (preferred) or low-dose ICS

plus an alternative controller medication. Severe persistent asthma included patients receiving moderate-dose ICS with alternative controller medication (preferred), or high-dose ICS with/without alternative controller medication, or the addition of oral systemic corticosteroids.

Varicella zoster virus infection (WT disease)

History and date of WT varicella disease were documented by a physician and routinely screened by parental questionnaire and physical exam.

Varicella vaccine

Patients were given two doses of the live attenuated varicella vaccine (Varivax, Merck and Company, Inc., West Point, PA, USA) according to the recommended schedule of the American Academy of Pediatrics.¹³ The first dose was given at 12–15 months of age. The second dose was given at 4–6 years of age, but may have been given earlier provided that it was at least 3 months after the first dose. Children 13 years or older received two doses at least 28 days apart according to the catchup immunization schedule.¹³

Statistical analysis

Statistical significance for age of asthma onset and asthma-varicella exposure interval was assessed using two-way analysis of variance with Scheffe multiple-comparison procedure. All calculations were performed using SPSS 10.0 Software (SPSS Inc., Chicago, IL). Statistical differences of asthma severity between the recombinant vaccine and WT disease groups were assessed using χ^2 square tests, as described in the figures. P values of < 0.05 were considered significant.

Results

Population characteristics

The characteristics of the study population are shown in Table 1. Pediatric patients diagnosed with asthma ($N = 62$) were divided into 4 groups, including patients who received the recombinant varicella vaccine (1) before ($n = 30$, 48%) or (2) after asthma onset ($n = 9$, 15%), and patients who had WT VZV infection (3) before ($n = 13$, 21%) or (4) after asthma onset ($n = 10$, 16%). Overall 63% of the patients were male; patients who received recombinant varicella vaccine before and after asthma were 57 and 78% male, respectively; patients who had WT VZV infection before and after asthma were 69% and 60% male, respectively. Patients were predominantly Caucasian (89%), but also included Hispanic (6%), Asian (3%), and African American (2%) (Table 1). There were no significant differences in the sex of the children in all groups (Table 1). The children were all up to date with other vaccinations, including Hepatitis A Virus, Hepatitis B Virus, Influenza, Inactivated Polio Vaccine, and Measles-Mumps-Rubella, according to the recommended vaccination schedule of the American Academy of Pediatrics.¹³

Age of onset and interval of exposure to WT VZV infection or varicella vaccine

There was no difference in the age of varicella antigen exposure between all patient groups, except patients who had WT

TABLE 1. DEMOGRAPHICS OF PATIENT SUBPOPULATIONS

Demographic	Recombinant vaccine		Wild-type infection		Total
	Before asthma onset	After asthma onset	Before asthma onset	After asthma onset	
Sex					
Male	17 (57%)	7 (78%)	9 (69%)	6 (60%)	39 (63%)
Female	13 (43%)	2 (22%)	4 (31%)	4 (40%)	23 (37%)
Race/ethnicity					
Caucasian	25 (83%)	9 (100%)	12 (92%)	9 (90%)	55 (89%)
African American	2 (7%)	—	—	—	2 (3%)
Hispanic	2 (7%)	—	1 (8%)	1 (10%)	4 (6%)
Asian	1 (3%)	—	—	—	1 (2%)
Age of recombinant vaccine (years)					
Mean $\pm$ SD	3.2 $\pm$ 3.0	2.2 $\pm$ 1.0	—	—	2.9 $\pm$ 2.7
Median	1.8	2.2	—	—	2.0
Low, high	1.0, 12.8	1.0, 3.8	—	—	1.0, 12.8
Age of wild-type VZV infection (years)					
Mean $\pm$ SD	—	—	4.4 $\pm$ 2.2	11.8 $\pm$ 5.3	7.5 $\pm$ 5.2
Median	—	—	4.4	9.8	5.7
Low, high	—	—	1.1, 9.0	5.5, 21.5	1.1, 21.5
Total	30 (48%)	9 (15%)	13 (21%)	10 (16%)	62 (100%)

infection after asthma onset, who were exposed at an older age (11.8 $\pm$ 5.3 years) (Table 1). However, patients who were diagnosed with asthma after WT infection developed asthma at a significantly later age (mean $\pm$ SD: 13.9 $\pm$ 6.5 years, median: 12.8 years) than patients who received the recombinant vaccine (mean $\pm$ SD: 5.0 $\pm$ 3.6 years, median: 4.3 years) ($P < 0.01$) (Fig. 1A). Moreover, patients who had WT infection before asthma onset developed asthma after a longer interval (mean $\pm$ SD: 9.4 $\pm$ 4.4 years, median: 9.5 years) than either patients who had WT infection after asthma onset (mean $\pm$ SD: 3.0 $\pm$ 1.7 years, median: 3.6 years) or patients who received recombinant vaccine (mean $\pm$ SD: 2.9 $\pm$ 2.0 and 0.8 $\pm$ 0.5 years, median: 2.5 and 0.8 years, respectively) ($P < 0.01$) (Fig. 1B).

Asthma classifications and severe flare-ups after WT VZV infection or varicella vaccine

Patients who developed asthma after recombinant vaccine were equally distributed within the NAEPP/EPR2 classification of intermittent, mild persistent, or moderate persistent (30.0%, 36.7%, and 33.3%, respectively; χ^2 with normal distribution, $\alpha > 0.1$) (Fig. 2). No patients in any of the groups were classified as severe persistent asthma. In contrast, patients who were diagnosed with asthma after WT VZV infection were predominantly classified as intermittent with less mild persistent and moderate persistent patients (61.5%, 15.4%, and 23.1%, respectively; χ^2 , $\alpha < 0.01$) (Fig. 2). Moreover, patients who were diagnosed with asthma after WT VZV infection had a lower number of severe asthma flare-ups requiring inhaled or oral corticosteroids ≤ 1 year (0.0%) and > 1 year after infection (30.8%) than patients who received

recombinant vaccine (21.4% and 48.3%, respectively) (χ^2 , $\alpha < 0.01$) (Fig. 3).

Similar asthma classifications were found in patients who received either recombinant vaccine (22.2%, 22.2%, and 55.6%) or had WT infection after asthma onset (10.0%, 30.0%, 60.0%; χ^2 , $\alpha > 0.1$). However, patients who had either recombinant vaccine or WT disease after asthma onset had worse asthma classifications than those exposed before asthma onset (χ^2 , $\alpha > 0.1$; Fig. 2). However, there was no difference in the number of severe asthma flare-ups requiring inhaled or oral corticosteroids ≤ 1 year or > 1 year after infection between patients who received recombinant vaccine (30.0% and 20.0%) or had a WT infection (44.4% and 33.3%) after asthma onset (χ^2 , $\alpha > 0.2$) (Fig. 3).

Allergies after WT VZV infection or varicella vaccine

Patients who had WT infection before asthma onset had decreased incidence of reported allergic symptoms (15.4%) and referral to an allergist or pulmonologist (7.7%) than patients who either had WT VZV infections after asthma onset (60.0%, 40.0%, respectively) or those who received recombinant varicella vaccine before asthma onset (36.7%, 33.3%, respectively), but similar incidence to patients who received recombinant vaccine after asthma onset (22.2%, 11.1%, respectively) (χ^2 , $\alpha < 0.001$) (Table 2). Patients who received varicella vaccine before asthma onset had a higher incidence of elevated serum IgE levels (> 100 IU/mL) (normal range in children: 20–100 IU/mL, Quest Diagnostics) than those that received varicella vaccine after asthma onset (26.7%, 11.1%, respectively), or that

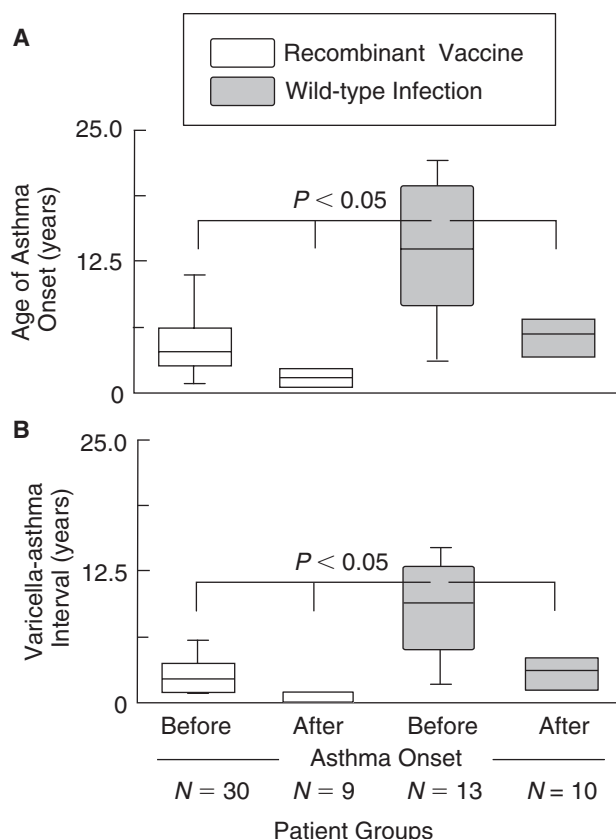


FIG. 1. Comparative analysis of (A) age of asthma onset and (B) varicella-asthma interval period in patients who either received varicella vaccine or had a wild-type varicella infection. Patients ($N = 62$) were diagnosed with asthma based on the NAEPP/EPR2 Guidelines. History and date of wild-type varicella disease were documented by physician and routinely screened by parental questionnaire and physical exam. Varicella vaccine was administered according to the recommended schedule of the American Academy of Pediatrics. Statistical significance was determined by two-way analysis of variance with the Scheffe *post hoc* method ($P < 0.05$).

had WT VZV infection before or after asthma onset (15.4%, 10.0%, respectively).

Discussion

In the present study, we provide further insight into the relationship between WT VZV infection or varicella vaccine and the onset of asthma. We observed that (1) VZV infection (before diagnosis of asthma) is associated with a later age of asthma onset and prolonged interval until development of asthma symptoms; (2) VZV infection has an asthma-protective effect even when occurring in late childhood and adolescence; (3) children with VZV infection that eventually develop asthma have decreased asthma symptoms, milder asthma classifications, and fewer severe asthma flare-ups; and (4) VZV infection is also associated with a lower prevalence of allergies. However, varicella vaccine was not

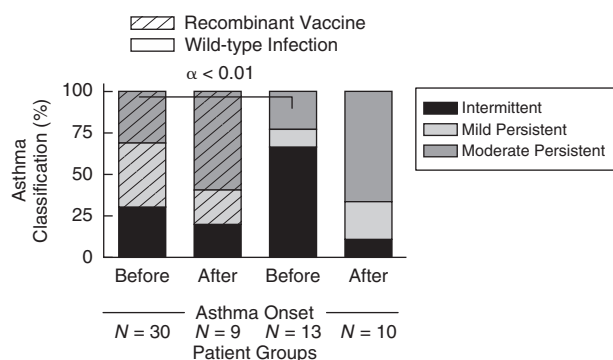


FIG. 2. Comparative analysis of asthma symptoms in patients who either received varicella vaccine or had a wild-type varicella infection. Asthma classification was determined according to the NAEPP/EPR2 Guidelines based on daytime, nighttime, and exertional symptom frequency. Statistical significance was determined using χ^2 analysis ($\alpha < 0.01$).

associated with the age or interval of asthma onset, asthma symptoms, or allergic history.

The present studies are the first to report that VZV infection is associated with a later age of asthma onset and prolonged interval until development of asthma symptoms. The results of these studies are consistent with the studies of Illi et al. that showed that children with more than one episode of varicella infection in the first 3 years of life were less likely to develop asthma by schoolage.⁹ Moreover, the results of our studies demonstrate that the protection of a single episode of WT VZV infection can extend well into adolescence.

Further, we found that VZV infection has an asthma-protective effect even when it occurs in late childhood or adolescence. These data suggest that the protective effect of VZV on asthma and allergy is not limited to early childhood. This is in contrast to the hypothesis that the asthma-protective effects of viral illnesses in children are attributable to the immature immune system found in the first year of life.^{9,14,15} However, this study is in agreement with previous studies in our laboratory that reported the presence of IgE anti-VZV antibodies and decreased total serum IgE levels after shingles infection.¹¹

One possible explanation is that the extended protection from asthma found in the present studies is specific to VZV infections. Varicella zoster virus infection has a unique pathogenesis that tracks from the respiratory tract to lymph nodes, ending at skin where it infects keratinocytes and can remain dormant indefinitely in cutaneous sensory neurons (reviewed in ref. 16). Moreover, it is thought that VZV directly infects immune cells, including peripheral T cells and monocytes (reviewed in ref. 16). Thus, it may indicate that VZV infection of immune cells may directly influence these cells to elicit protection from asthma and/or allergies.

Alternatively, it is possible that a severe, protracted viral illness of other etiologies would also provide extended protection from the development of asthma. Support for this hypothesis comes from the findings of the present studies that the live attenuated varicella vaccine does not elicit

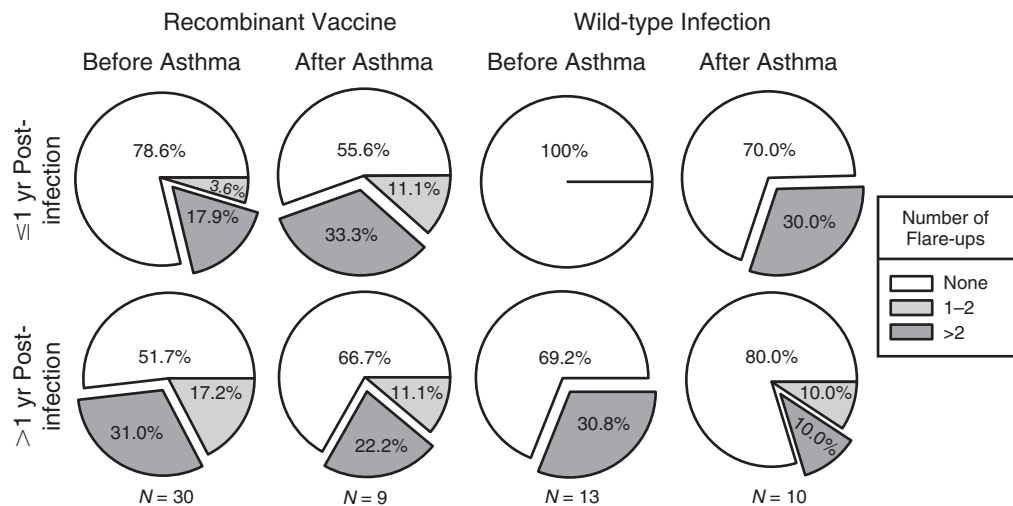


FIG. 3. Comparative analysis of frequency of severe asthma flare-ups in patients who either received varicella vaccine or had a wild-type varicella infection. Severe asthma flare-ups were diagnosed and treated according to the NAEPP/EPR2 Guidelines. Statistical significance was determined using χ^2 analysis ($\alpha < 0.01$).

similar protection from asthma and allergy, despite its induction of robust innate and memory immune responses.¹⁷ This is consistent with the idea that a subclinical VZV infection may not offer protection from asthma and allergy. However, much of the details of the immune responses elicited by the vaccine and WT infection remain undefined.

The present studies also found that children with VZV infection that eventually develop asthma have decreased asthma symptoms, milder asthma classifications, and fewer severe asthma flare-ups. Our study adds another dimension by demonstrating that VZV infection both decreases the likelihood of developing asthma and delays asthma onset by months to years that it would also decrease subsequent asthma symptoms. However, our data indicate that the protection of viral illnesses from the development of asthma is not an all-or-nothing process that turns off atopy. Rather, the protective effect of viral infections appears to be the result of inhibition of inflammatory responses. Thus, even if the child goes on to develop asthma, the symptoms are more mild and less often.

The current studies also found that VZV infection is associated with a lower prevalence of allergies. This is consistent with previous studies that have demonstrated decreased

allergies after a variety of viral infections.¹⁻⁴ This suggests that VZV infection may cause inhibition of IgE production thereby suppressing the development of atopy and possibly even improving existing atopy.

We are aware of some limitations inherent to this study; that is, it is a retrospective/observational study and involves a small number of patients. To address this issue, we used the Scheffe *post hoc* analysis procedure, which is the most stringent method to compensate for the effects of smaller groups with unequal sample size.¹⁸ Moreover, it is also a time-sensitive study, since the number of children with WT VZV has decreased over the years, since the introduction of the varicella vaccine; this group of patients is relatively small. Finally, asthmatic patients who had neither recombinant vaccine nor WT infection, another important control group, were not found in the patient population. Despite the obvious limitations of our study, we still found significant differences between the vaccine and WT infection groups.

Conclusions

The findings of this study help to further elucidate the protective role of VZV infection against asthma and atopy.

TABLE 2. DISTRIBUTIONS OF ALLERGIC HISTORY AND OTHER MISCELLANEOUS DISEASES

Group	History of allergies (%)	Referral to allergist (%)	Elevated serum IgE levels (%)	Other diagnoses
Recombinant vaccine				
Before asthma onset	36.7%	33.6%	26.7%	Allergic rhinitis, atopic dermatitis, eczema, febrile seizures
After asthma onset	22.2%	11.1%	11.1%	Allergic rhinitis
Wild-type infection				
Before asthma onset	15.4% ^a	7.7% ^a	15.4%	Allergic rhinitis
After asthma onset	60.0%	40.0%	10.0%	Eczema, rubeola

^a χ^2 , $\alpha < 0.001$.

In addition, these findings suggest a novel mechanism of inhibition of inflammatory immune responses that has yet to be described. The protective effect of VZV infection may have implications for other viral infections that are associated with asthma and help us further understand the relationship between viral infection(s), asthma, and allergy. Future larger prospective studies are needed to better define the relationship between VZV and asthma, which would help establish recommendations concerning care of these patients.

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