

Virus-Provoked Rhinitis in Patients Who Have Allergies

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ABSTRACT

The most common illnesses in humans are the respiratory tract infections caused by viruses. When limited to the upper respiratory region, these infections often are designated as "a common cold." Viruses commonly associated with these upper respiratory infections (URI) include rhinoviruses (RVs), respiratory syncytial virus, influenza virus, parainfluenza virus, corona virus, and adenoviruses. Clinical observations have suggested that patients with allergic rhinitis and asthma experience more pronounced symptoms during a viral URI than patients who do not have allergies and who are infected with the same virus under similar circumstances. Using an experimental virus infection model in human volunteers with and without allergic rhinitis, several groups of clinical investigators have studied the effects of experimental RV infections. These observations indicate that the experimental virus infection may induce host responses that provoke enhanced immunoglobulin E (IgE) synthesis. Whether this translates into enhanced symptoms has been suggested in one study but not in another. This article will review these studies, which suggest that it is the host response to the virus and not the virus itself that plays the major role in symptom pathogenesis. (Allergy and Asthma Proc 23:99–102, 2002)

Virus provoked respiratory tract infections are the most common illnesses in humans. When limited to the upper respiratory tract, these viral infections often are re-

ferred to as a "common cold." The viruses implicated in the pathogenesis of the "common cold" include rhinoviruses (RVs), respiratory syncytial virus, influenza virus, parainfluenza virus, coronavirus, and, less commonly, adenoviruses. These viruses not only cause uncomplicated viral rhinitis, but also contribute to complications or exacerbations of other respiratory tract illnesses including asthma, sinusitis, and otitis.^{1–3} There is great individual variability in not only the symptoms of viral rhinitis, which includes rhinorrhea, sneezing, nasal obstruction, sore throat, cough, malaise, and fever, but also the development of the potential complications including asthma, sinusitis, and otitis. The variability of disease expression may be caused by characteristics of the virus, the host, or the host responses. The pathogenesis, pathophysiologies, and complications of viral rhinitis have been studied using epidemiological surveys, natural infection, animal models, and adults experimentally infected with different respiratory viruses. The distinct advantages offered by the experimental infection challenge model over natural infection is its ability to control several variables: the health of the subject, the subject's preexisting immune responses to the virus, and other environmental exposures such as allergens, the dose of the virus, the temporal sequence of virus shedding (i.e., infection), symptoms, signs, pathophysiologies of the nose, lungs, and ears, as well as the elaboration of the various cytokines and mediators of inflammation. Despite the use of standardized lots of virus inoculum, inoculation techniques and enrollment of susceptible subjects for the experimental infection study protocols, there has been individual variability in the severity of the respiratory symptoms and its complications. The preexisting level of specific viral antibody can modulate the severity of symptoms and viral shedding after experimental infection but cannot account for all the variability observed.⁴

Prospective epidemiological surveys have implicated an association between expression of allergy, documented by elevated levels of serum immunoglobulin E (IgE) and positive allergy skin tests with the development of asthma in

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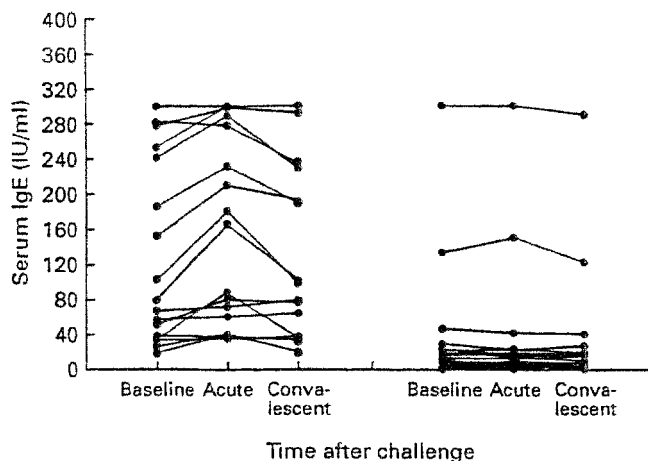


Figure 1. Total serum IgE concentrations before (baseline), during (acute), and after (21 days convalescent) RV39 experimental virus infection in subjects with allergic rhinitis (AR; $n = 20$) and subjects who did not have allergic rhinitis ($n = 18$). The subjects with allergic rhinitis manifested increased serum IgE during the acute virus infection and these IgE levels returned toward the baseline values 21 days later. This increase in serum IgE was not observed in the subjects who did not have allergic rhinitis (source: Ref. 8, reproduced with permission).

infants and children who manifested viral illnesses that provoked wheezing and rhinitis.⁵ In addition, clinical observations and anecdotal experiences have indicated that patients with allergic rhinitis experience more pronounced symptoms during a viral upper respiratory infection (URI) than those individuals similarly infected with a respiratory virus who do not have allergic rhinitis.⁶ To attempt to better define the relationships between viral rhinitis and allergy, several groups of investigators have studied the effects of experimental virus infection in human volunteers with and without allergic rhinitis. This presentation will review those observations.

EXPERIMENTAL VIRUS INFECTION AND THE UPPER AIRWAY

Studies in our laboratories reported by Doyle and colleagues examined experimental nasal infection with RV39 in volunteers with and without a history of seasonal

allergic rhinitis, which was confirmed by positive IgE antibody tests.⁷ All 38 subjects were infected successfully as documented by viral shedding or rise in specific antibody 21 days after infection. All but six subjects developed typical cold symptoms that peaked on days 3 and 4 and were subsiding by day 7. The subjects with allergies had an earlier onset of sneezing on day 1, but there were no statistical differences in the magnitude, frequency, or duration of overall symptoms as well as the individual symptoms of sneezing, congestion, and pruritus, as well as nasal secretion weights. The pathophysiological measurements of rhinomanometry and cilia function as measured by saccharin clearance were similar in both subjects with allergies and subjects without allergies in magnitude, frequency, and time of onset. However, there was an earlier onset of eustachian tube obstruction on day 2 in the subjects with allergies but the frequency and duration of the eustachian tube obstruction was similar in both cohorts. Although the clinical symptoms were similar in subjects with and without allergies, there were some allergy-related differences in the serologic and cellular immune responses to the RV39 infection. As shown in Fig. 1, total serum IgE levels increased significantly in the RV39-infected patients who had allergies but not in the RV39-infected subjects who did not have allergies.⁸ These same RV39-infected patients who had allergies had increased leukocyte histamine release in vitro after inoculation with anti-IgE as compared with the subjects who did not have allergies.⁸ In addition, peripheral blood mononuclear cells from subjects with allergies had a lower baseline proliferation response to RV39 but both groups had vigorous responses 3 weeks after viral inoculation.⁹

The effect of RV39 infection on nasal responsiveness to histamine and cold air was studied also in these same subjects.¹⁰ Provocation to intranasal histamine was performed 6–8 weeks before RV inoculation and then again 8–13 days after RV inoculation. After intranasal histamine challenge but before RV39 infection the subjects with allergies had twice as much sneezing, rhinorrhea, and secretions but similar conductance by rhinomanometry as compared with the subjects who did not have allergies (Fig. 2). The RV39 infection provoked dramatic increases in both

	Response to Intranasal Histamine Provocation			
	Before RV ₃₉ Infection		After RV ₃₉ Infection	
	Allergic	Non-allergic	Allergic	Non-allergic
Sneeze count (no.)	10.0 ± 12.4	4.9 ± 4.6	19.5 ± 15.4	10.5 ± 8.2
Rhinorrhea symptoms	5.3 ± 3.9	2.3 ± 2.3	6.7 ± 3.1	3.3 ± 2.6
Secretion Weight (gm)	3.6 ± 2.5	1.3 ± 1.2	7.8 ± 5.7	5.7 ± 2.8
Congestion Symptoms	6.0 ± 2.7	4.7 ± 1.5	5.6 ± 2.8	3.2 ± 2.3
Conductance (l/sec/cw/t ₂₀)	1.0 ± 0.5	1.2 ± 0.7	0.9 ± 0.5	1.0 ± 0.4

Figure 2. Allergic subjects after intranasal histamine challenge had approximately twice as many sneezes, rhinorrhea symptoms, secretions by weight, and congestion symptoms as compared to subjects without allergies, whereas nasal airflow as expressed as conductance was comparable in subjects with versus subjects without allergies. After RV39 infection subjects with and without allergies had significant increases in sneeze counts and secretion weight. RV39 infection had little effect on nasal airflow or congestion symptoms (source: Ref. 10, reproduced with permission).

allergic and nonallergic nasal symptoms. RV39 infection in our studies did not provoke changes in lung function in either the subjects who had allergies or the subjects who did not have allergies as measured by spirometry or methacholine challenge.¹¹

Barodin and coworkers also have experimentally infected subjects with and without allergies but they used a different RV (RV16).¹² They studied 22 subjects, which included 11 nonatopic, 5 atopic, and another 6 atopic subjects who also had asthma. After intranasal challenge, all subjects were infected as documented by viral shedding (culture) and 17 of the individuals developed cold symptoms. Neutralizing RV16 antibody unexpectedly developed in 10 subjects between screening and intranasal RV16 inoculation and the presence or absence of this antibody was associated with subsequent severity of cold symptoms in the normals, but this was not so in the subjects with allergies. In the presence of neutralizing RV16 antibody, the subjects who did not have allergies had mild symptoms in contrast to the subjects with allergies who developed severe cold symptoms. This differential response was matched by nasal wash albumin levels, which were significantly increased during the cold in the patients with allergies but not in the subjects who did not have allergies, with increased preinoculation antibody levels. Both subjects with and without allergies who were antibody negative developed severe colds. This study also suggested that subjects with allergies were predisposed to develop more severe symptomatic colds.

These several studies using the intranasal experimental virus infection described previously were conducted out of the relevant pollen season and the subjects were asymptomatic before virus inoculation. Avilla and coworkers proposed that inducing allergic inflammation just before RV inoculation would amplify the local response to infection in subjects with allergies. Before inoculation with RV16, one group of 10 subjects with allergies had three intranasal challenges with allergen and another group of 10 subjects with allergies received three placebo challenges in the week before experimental intranasal infection with RV16. The two groups had equal rates (90%) of infection and similar cold symptoms but the inoculation period was longer and cold symptoms did not last as long in the allergen-challenged group. There were no changes in lung spirometry or methacholine provocative tests in either group during or after RV16 infection. Thus, this study showed that priming the nasal mucosa with repeated allergen challenges before RV16 experimental intranasal infection did not worsen the severity of cold symptoms but delayed their onset and shortened the duration. This study also showed that there was a delayed appearance and an increase in nasal cytokine secretion of interleukin-6 (IL-6) and IL-8 that paralleled the delayed appearance of cold symptoms and corroborates the concept that the host response not the virus causes cold symptoms.¹³

SUMMARY

Viral respiratory infections have major impacts on upper respiratory function as well as lower respiratory function in patients of all ages. These viral illnesses, which often are mild and only an inconvenience to many normal individuals, also can influence the subsequent development of allergy and asthma exacerbations with a major influence on these patient's well-being and their health status. Lower airway infection with respiratory syncytial virus increases the risk of asthma during the first 10 years of life, especially in those infants who have a genetic allergic predisposition. Yet, overall, the respiratory infection burden, the so-called "hygiene hypothesis," as a whole probably is protective against the development of allergic rhinitis and asthma. However, once asthma has developed, respiratory viruses precipitate many of the asthma exacerbations seen in both children and adults.

RV is the most common viral cause of URI and lower respiratory tract infections in older children and adults. Because allergy increases the risk of wheezing during a viral respiratory tract infection, our group of investigators, as well as other investigators, has focused on the interactions between allergic inflammation and experimental viral infection to understand the pathogenesis of these allergic and asthmatic exacerbations. In this article, I have discussed studies of experimental RV infection in humans with and without allergies. During an experimental RV infection the allergic inflammatory responses as reported by Skoner *et al.* showed that allergic IgE responses were potentiated by experimental RV infection in subjects with allergic rhinitis even though significant increases of nasal symptoms were not seen. Despite these observations, experimental RV infections in subjects who have and who do not have allergies causes far less of both upper and lower airway disease than clinicians would have anticipated based on the frequency that RV causes significant asthmatic exacerbations.

Although the precise mechanism by which respiratory viruses such as RV cause symptoms are not known, there is evidence that the host immune response to the virus but not the virus itself plays a major role in symptom pathogenesis. Viral replication in the epithelium of the airway triggers intracellular signaling pathways leading to increases in the local secretion of multiple cytokines, chemokines, and adhesion molecules. It appears that there may be increases in various cytokines during viral infection that can potentially recruit and activate those aspects of inflammation that are linked to the expression of allergy or asthma. It is anticipated that future studies in these aspects of viral and allergic inflammation will lead to a better understanding of the pathogenesis of both viral and allergic rhinitis and asthma.

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