Virus-provoked rhinitis and asthma in allergic patients

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Summary

Rhinovirus, influenza, parainfluenza or respiratory syncytial virus not only provoke upper respiratory tract infections (URI) but also can precipitate asthma in adults and children, many of whom also manifest allergic respiratory disease. It has been postulated that patients with allergic rhinitis experience more pronounced symptoms and pathophysiology during URI than individuals without allergy. These observations have provided limited insight into the pathogenesis of URI in allergic patients. To better define these relationships several groups of investigators have examined the effect of experimental virus infection on volunteers with and without allergic rhinitis and with and without asthma. Lemanski et al. showed that Rhinovirus 16 (RV16) was able to modify bronchial hyperreactivity and late phase allergic asthmatic reactions. Calhoun et al. demonstrated that RV16 potentiated airway inflammation after segmental allergen bronchoprovocation in allergic subjects. Experimental RV16 infection also provoked a modest increase in histamine responsiveness accompanied by a modest increase in bronchial and intranasal lymphocytes and eosinophils. Yet, experimental RV16 infection did not trigger asthma or changes in spirometry or changes in bronchial reactivity to histamine or bradykinin in normal subjects. Studies in our laboratories using experimental Rhinovirus 39 (RV39) infection did not alter pulmonary measurements or methacholine responses in normal healthy allergic subjects. These results were surprising, as enhanced WBC histamine release was observed in the same RV39-infected allergic subjects and was similar to that observed in RV16 infection described by others. The RV39-infected allergic subjects also showed acute increases in serum IgE as well as changes of cellular immune parameters. Bardin et al. described more severe nasal symptoms as well as increased nasal albumin in allergic rhinitis subjects experimentally infected with RV16. However, allergic subjects infected with RV39 did not show a physiologic hyper-responsiveness during a nonallergy season. Analysis of nasal secretions during RV39 infection did show more vascular permeability in allergic subjects. Experimental infection with RV39 and Influenza A has provoked eustachian tube obstruction, otitis media and rarely acute otitis. These studies of volunteers experimentally infected with virus suggest that atopy alone does not predispose to more severe symptoms but combining URI with allergen exposure enhanced allergen-induced inflammation. Recent studies implicate cytokines as participants in these virus-provoked responses. Increases in nasal lavage concentrations of IL-6 were found during experimental URIs caused by RV59, Influenza A and respiratory syncytial virus and coincide with peaks in symptomatology and pathophysiology. Moreover, IL-6 applied directly to the nasal mucosa in noninfected allergic subjects reproduced symptoms of rhinitis. Other studies have shown that IL-10 secretion from peripheral blood white cells was impaired in allergic subjects after experimental infection with Influenza A. It is anticipated that future studies using natural infection as well as experimental virus infection model will further define the mechanisms and relationships of virus infection to allergy and asthma.

Keywords allergic rhinitis, asthma, experimental virus infection, rhinovirus, viral RRI

Introduction

Virus-provoked respiratory tract infections are the most common illnesses in humans. When limited to the upper respiratory tract, these viral infections are often referred to as a ‘common cold’. The viruses implicated in the pathogenesis of the ‘common cold’ include rhinoviruses (RV), respiratory syncytial virus (RSV), influenza virus (IV), parainfluenza virus (PIV), coronavirus (CV) and, less commonly, adenoviruses (AV).

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 not only in the symptoms of the viral rhinitis, which include
rhinorrhea, sneezing, nasal obstruction, sore throat, cough, malaise and fever, but also in the development of the potential complications, including asthma, sinusitis and otitis. The variability of disease expression may be due to characteristics of the virus, the host or the host responses.

The pathogenesis, pathophysiology, 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 pre-existing 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, pathophysiology 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 enrolment 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 pre-existing 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 epidemiologic surveys have implicated an association between expression of allergy, documented by elevated levels of serum IgE and positive allergy skin tests with the development of asthma in infants and children who manifested a 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 URI than those individuals similarly infected with a respiratory virus who do not have allergic rhinitis [6].

In order to attempt to better define the relationships between viral rhinitis, asthma and allergy, several groups of investigators have studied the effects of experimental virus infection in human volunteers with and without allergic rhinitis and with and without asthma. This article 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 Rhinovirus 39 (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 successfully infected as documented by viral shedding or rise in specific antibody 21 days after infection. All but six developed typical cold symptoms, which peaked on days 3 and 4 and were subsiding by day 7. The allergic subjects had an earlier onset of sneezing on day 1, but there were no statistical differences in the magnitude, frequency, or duration of the overall as well as individual symptoms of sneezing, congestion and pruritus, and nasal secretion weights. The pathophysiological measurements of rhinomanometry and cilia function as measured by saccharin clearance were similar in both allergies and nonallergics in magnitude, frequency and time of onset. However, there was an earlier onset of eustachian tube obstruction on day 2 in the allergic subjects although the frequency and duration of the eustachian tube obstruction was similar in both cohorts.

Although the clinical symptoms were similar in both allergic and nonallergic, 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 allergic RV39-infected patients but not in the nonallergic RV39-infected subjects [8]. These same RV39-infected allergic patients had increased leucocyte histamine release in vitro after inoculation with anti-IgE as compared with the nonallergics [8]. In addition, peripheral blood mononuclear cells from allergic subjects 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 also studied in these same subjects [10]. Provocation to intranasal histamine was performed 6–8 weeks before and then again 8–13 days after RV inoculation. After intranasal histamine challenge but before RV39 infection the allergic subjects had twice as much sneezing, rhinorrhea and secretions but similar conductance by rhinomanometry as compared with the non-allergics (Table 1). The RV39 infection provoked dramatic increases in both allergic and nonallergic nasal symptoms. RV39 infection in our studies did not provoke changes in
Table 1. Response to intranasal histamine provocation

|                   | Before RV39 infection | After RV39 infection |
|-------------------|------------------------|----------------------|
|                   | Allergic | Nonallergic | Allergic | Nonallergic |
| 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 | 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/s/cmH2O) | 1.0 ± 0.5 | 1.2 ± 0.7 | 0.9 ± 0.5 | 1.0 ± 0.4 |

Allergic subjects after intranasal histamine challenge had approximately twice as many sneezes, rhinorrhea symptoms, secretions by weight and congestion symptoms as compared to nonallergic subjects whereas nasal airflow as expressed as conductance was comparable in allergic vs. allergic subjects. After RV39 infection allergics and nonallergics had significant increases in sneeze counts and secretion weight. RV39 infection had little effect on nasal airflow or congestion symptoms. Reprinted with permission from Doyle et al. (1994) [10].

Bardin and coworkers have also experimentally infected allergic and nonallergic subjects but used a different rhinovirus, Rhinovirus 16 (RV16) [12]. They studied 22 subjects, including 11 nonatopics, five atopics and another six atopics 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 normal subjects, but not so in the allergic subjects. The nonallergic subjects in the presence of neutralizing RV16 antibody had mild symptoms, in contrast to the allergies with neutralizing RV16 antibody who developed severe cold symptoms. This differential response was matched by nasal wash albumin levels, which were significantly increased during the cold in the allergies but not in the nonallergics with increased preinoculation antibody levels. Both allergies and the nonallergics who were antibody negative developed severe colds. This study also suggested that allergies were predisposed to develop more severe symptomatic colds.

These several studies using intranasal experimental virus infection described above were conducted out of the relevant pollen season and the subjects were asymptomatic prior to virus inoculation. Avila and coworkers proposed that inducing allergic inflammation just before RV inoculation would amplify the local response to infection in allergic subjects. Prior to inoculation with RV16, one group of 10 allergies had three intranasal challenges with allergens and another group of 10 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 in the allergen-challenged group and the duration of cold symptoms was shorter. 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 allergens challenged 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 increase in nasal cytokine secretion of IL-6 and IL-8 that paralleled the delayed appearance of cold symptoms and corroborates the concept that it is the host response and not the virus that causes cold symptoms [13].

Experimental virus infection and the lower airway

Lemanski and coworkers studied the effect of experimental RV16 infection on lower airway pathophysiology in 10 patients with allergic rhinitis [14]. There was a moderate increase in airway responsiveness to histamine at 48 h with the onset of the acute viral respiratory infection. In addition, RV39 infection increased the immediate response to allergen challenge as shown by a decrease in the concentration of allergens required to decrease the FEV1 by 20% (Fig. 2). Before virus inoculation only one subject had a late phase asthmatic reaction as indicated by a decrease in FEV1 of greater than 15% at 4–6 h postallergen challenge. However, in these same subjects after viral infection eight of the 10 subjects developed a late-phase reaction after allergen challenge. The same laboratory confirmed these observations in an additional eight subjects and also showed an enhanced increase in plasma histamine levels after allergen challenge [15]. These investigators hypothesized that RV infections promoted the development of the allergic reaction by increasing those hose responses that produced the early- and late-phase allergic reaction to allergens. Using segmental pulmonary allergen challenge in normal and allergic rhinitis patients who were infected with RV16, bronchoalveolar lavage (BAL) fluid analysis
before and after RV16 experimental infection showed an increase in BAL histamine, leucocytes and eosinophils [16]. The increased secretion of histamine persisted 4–6 weeks after the RV infection. Additional studies comparing patients with and without allergic rhinitis demonstrated that the lower airway response to histamine broncho-provocation was significantly different in allergic rhinitis subjects [17]. As shown in Fig. 3, there was also a positive correlation between the initial FEV₁ and the response to histamine provocation, indicating that the RV16 infection tended to increase the response to histamine provocation in those allergic rhinitis subjects with lower baseline FEV₁. Fraenkel and colleagues experimentally infected allergic and normals and showed that RV16 increased histamine responsiveness in those with allergic asthma, but the changes were moderate [18]. Similar observations were seen in another study by the same group with airway hyperresponsiveness selectively enhanced in the allergic subjects but not in the nonallergic subjects [19]. However, not all studies using experimental RV infection have shown consistent effects in airway hyperresponsiveness. Skoner and coworkers in our laboratories studied methacholine airway hyperresponsiveness in 31 subjects with allergic rhinitis and 27 normal controls experimentally infected with RV39 and found no effect of RV infection on the bronchial response to methacholine. Additional studies by Skoner et al. showed no effect of an attenuated influenza virus on lower airway function or bronchial responses to methacholine in either allergic or nonallergic [20]. Halperin and colleagues experimentally infected 19 asthmatic subjects with RV39 and Rhinovirus Hanks and found changes in airway hyper-responsiveness to histamine in only four of the 19 subjects [21]. These four subjects who developed histamine hyperresponsiveness during RV infection also had some decrease in FEV₁, which might have some clinical significance. In another study this time using experimental RV2 infection Summers and colleagues found no changes in airway hyperresponsiveness to either histamine or bradykinin regardless of their allergic status [22]. Additional studies by Fleming et al. of RV16 experimental infection in healthy and asthmatic subjects also showed the severity of cold symptoms and the relative changes in pulmonary function to be similar in both groups, with only small increases in asthmatic symptoms and no increase in the use of bronchodilators [23].

**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 are often mild and only an inconvenience to many normal individuals, can also 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 decade 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 is probably protective against the development of asthma. However, once asthma has developed, respiratory viruses precipitate many of the asthma exacerbations seen in both children and adults.
Rhinovirus is the most common viral cause of upper respiratory 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 have focused on the interactions between allergic inflammation and experimental viral infection to understand the pathogenesis of these allergic and asthmatic exacerbations. In this review article I have discussed studies of experimental RV infection in both allergic and nonallergic humans. Allergen challenge during an experimental RV infection enhances the allergic and asthmatic inflammatory responses as reported by Lemanski and coworkers, who showed that the combination of allergen and RV in allergic subjects will enhance lower airway 'asthmatic-like' pathophysiology [14]. 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 [8]. In spite of these observations, experimental RV infections in allergic and nonallergic subjects 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 is not known, there is evidence that the host immune response to the virus but not the virus itself plays a major role in symptoms pathogenesis. Viral replication in the epithelium of the airway triggers intracellular signalling 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 allergic rhinitis and asthma.

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