Human rhinoviruses, allergy, and asthma: a clinical approach

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Summary. The prevalence of allergic diseases is increasing in Lithuania as in the world. The prevalence of allergic sensitization is often higher than 50% of the population. The “hygiene hypothesis” proposed that reduced immune-stimulation by infections may have resulted in the more widespread clinical expression of atopic disease. However, it alone does not provide an adequate explanation for the observed increase of allergic diseases. Human rhinovirus infections are the major infections with a worldwide distribution. Viral infections of the respiratory tract are the most common triggers of acute asthma exacerbations. These exacerbations are poorly responsive to current asthma therapies and new approaches to therapy are needed.

The aim of this review is to present the current knowledge and clinical implications of human rhinovirus infection in allergy and asthma development and needs for further research. Recent evidence has shown that the immune responses to human rhinoviruses differ between asthmatic and nonasthmatic subjects. Novel insights into the mechanisms of virus-induced asthma exacerbations support the possibility that viral infections may be involved in the epithelial cells damage, inflammation, and airway hyperresponsiveness as well as in profibrotic response and induction of airway remodeling. The data of original investigations support the concept that the immune stimulation by rhinovirus infections contributes to the development of asthma, when an atopic host is infected with human rhinoviruses. Early rhinoviral wheezing is the predictor of subsequent asthma development in high-risk children. Synergistic effect of allergic sensitization, allergen exposure, and viral infection was suggested in the increased risk of hospitalization for asthma in both children and adults. Timing of allergen exposure may be important in a synergistic outcome. The increased susceptibility to rhinovirus infections was identified in atopic asthma. This review also presents the current options on the treatment and prevention of virus-induced asthma.

Further studies are needed in order to differentiate between the response to viruses of healthy and atopic or nonatopic asthmatic children and adults. New research data may lead to novel strategies in treatment and prevention of asthma exacerbations as well as prevention of asthma induction.

Introduction

The prevalence of allergic and autoimmune diseases is increasing in the world. IgE sensitization against allergens showed a steep increase of up to 50% in the population together with an increase in clinical allergic disease of up to 30% in some communities, particularly during the past three decades (1). Asthma and allergies have become increasingly prevalent over the last few decades across the WHO European region, with an average of more than 10% of children suffering from asthmatic symptoms. The epidemiologic research on asthma and allergic diseases such as the International Study on Asthma and Allergies in Childhood (ISAAC) has demonstrated that prevalence of asthma and allergic rhinoconjunctivitis is increasing through the world and in Lithuania, which is a participant of this study (2). Children and adolescents wheeze is 5-fold more frequent (10.1%) than asthma diagnosis (2.2%) in Lithuania and in other countries of European Union-25 according to the prevalence data.
The purpose of this review is to summarize the recent changes in our understanding of the epidemiology, clinical significance of human rhinovirus (HRV) infection and the role in the pathogenesis of allergy and asthma that have occurred as a result of the improved diagnostic sensitivity provided by the polymerase chain reaction (PCR) assays.

**The “hygiene hypothesis” for the increase in prevalence of allergic diseases**

One of the major hypotheses, which may operate in an increasing prevalence of allergic and autoimmune diseases, is the so-called “hygiene hypothesis” (4). According to this theory, a lot of hygiene and a lack of contacts with infections contribute to the development of allergies. To fully investigate the “hygiene hypothesis,” the investigators need to understand how host immune responses to infections can influence the developing immune system. Repeated mild infections in early life may have a protective role in the development of asthma or atopy by driving the immune system toward Th1 responses (5). Studies of infection exposure in early life would also consider whether allergen exposure preceded, was concomitant, or followed such infection. A recent study in two UK birth cohorts found that none of the clinically apparent infections considered appear to have an important role in allergy prevention, and none of 30 infectious illnesses investigated had strong or consistent associations with hay fever (6). Epidemiological studies provide no consistent support for either a beneficial or adverse effect of vaccination/immunization on atopic tendency (4). It has been suggested that there is no evidence for an increased risk of allergic diseases associated with childhood vaccinations. The “hygiene hypothesis” alone cannot explain the increasing prevalence of allergic diseases. The prevalence of asthma is increasing among children who live in very poor housing (7, 8). A lot of questions remain unresolved, regarding the nature and difference of protective and triggering infections, the mechanisms of protection and the spectrum of diseases (1, 2, 9, 10).

**The epidemiology of human rhinovirus infections**

HRVs are the major cause of the common cold, one of the most frequent infectious diseases in humans, and also one of the commonest triggers of acute asthma exacerbations (11, 12). HRVs were first isolated from individuals with common colds by Pelon et al. and Price in 1956. In 50 years since that discovery, more than 100 serotypes of HRVs have been described, the crystallographic structure of the outer shell has been solved, and the genome has been sequenced (13, 14). Children with recurrent respiratory infections (RRIs) are not affected by severe disorders of the immune system. RRIs represent essentially the consequence of an increased exposure to infectious agents during the first years of life, when immune functions are still largely immature (15). The epidemiology of HRV infections was initially described several decades ago in a series of studies that relied on cell culture isolation for detection of virus. These studies not only defined the fall and spring as the seasonal peaks of HRV infection but also revealed a substantial incidence of infection in the summer and winter months (16). Loens et al. (17) demonstrated that nucleic acid sequence-based amplification (NASBA) was equal to that in tissue culture (on RV-15). The widespread use of PCR for detection of rhinovirus has revealed a surprisingly high incidence of asymptomatic infection. Several studies have found that 12–22% of samples from asymptomatic individuals were positive for HRVs (14, 18). These observations in the natural setting are consistent with observations in the experimental challenge model of infection in which 20–30% of infected volunteers were asymptomatic. Viral RNA is reported to be detectable in nasal secretions for 2–3 weeks prior to illness and for 4–5 weeks after infection (14). Overall, a virus infection was detected by real-time PCR in about 80% of reported illnesses with lower respiratory manifestations (cough, wheezing, shortness of breath) or falls in peak expiratory flow rates, including the exacerbations in asthmatics (50–79%) and wheezing in hospitalized children (45–65%) (19, 20). A study of 179 asthmatic children with exacerbations hospitalized during two winter and two spring/summer seasons detected HRV RNA in nasopharyngeal aspirates in 79%, a significantly greater proportion than the observed frequencies of 17% in 29 asymptomatic asthmatic children and 52% in 50 nonasthmatic ambulatory children with upper respiratory tract illness (21). Malmstrom et al. evaluated the presence of HRV in the lower respiratory tract by obtaining bronchial biopsies from infants with
recurrent asthma-like respiratory symptoms and detected HRV in 45% of specimens. Abnormal lung function was found in 86% of HRV-positive infants and in 58% of HRV-negative infants (22). Innovative methods now in development make it interesting to pursue new therapies to “catch” this elusive and perfectly adapted pathogen (13).

**Variations in pathogenicity among human rhinoviruses**

HRVs are members of the Picornaviridae. A total of 102 serotypes of HRVs have been identified. There are two groups of HRVs depending from the receptor utilization. More than 90% belong to the major group family. HRVs are nonenveloped viruses with an icosahedral capsid enclosing a single-stranded, positive-sense RNA genome (12).

The observation of a new rhinovirus genotype in the context of an unusual clinical syndrome raises the possibility that biologic variation in the virus may be associated with variation in clinical manifestations (23). This possibility is also suggested by a recent study (24) that characterized the epidemiology and clinical manifestations of a newly described HRV. Picornavirus was detected by PCR in 346 (41%) of 1244 specimens from nasopharyngeal aspirates collected from patients with acute respiratory infections in this study. Seventeen patients were infected with a novel rhinovirus designated HRV-QPM, and 11 (65%) of these 17 patients, including five infants with bronchiolitis, had lower respiratory tract symptoms (24). Kistler et al. (25), using a new microarray-based technology, detected HRVs in 37 (45%) of 82 specimens from adults with acute respiratory illness. Five of the isolates represented a distinct genetic subgroup of HRVs, although in this study, the clinical manifestations of the infections caused by the new subgroup were indistinguishable from those caused by other virus genotypes. The ability of these new techniques to distinguish amongst different HRV strains provides an opportunity to evaluate the association between genetic changes in the virus and clinical manifestations of illness (14).

**Clinical evidence for the association of human rhinoviruses, allergy, and asthma exacerbation**

Viral infections are important causes of wheezing among children with a confirmed history of asthma. Viral infections were identified as the cause in 60–85% of acute exacerbations of wheezing and asthma exacerbations in both children and adults (14, 26–28). HRVs are responsible for about two-thirds of these infections (29). Allergen-induced events are less frequent, but much less is known about the mechanisms of virus-induced asthma exacerbations (30, 31). Both a fall peak of asthma exacerbation and the fall increase in the incidence of HRV infection have been reported in association with the beginning of the school year (29). The timing of the asthma peak may be due to a convergence of HRV infection spread among school children and seasonal allergen exposure. Timing of birth in relationship to winter virus season confers a differential and definable risk of developing early childhood asthma, establishing winter virus seasonality as a causal factor in asthma development. Delay of initial exposure or prevention of winter viral infection during early infancy could prevent asthma (32). The strong association of HRV infection with asthma exacerbation suggests that prevention or treatment of the HRV infections may be an effective approach for the prevention of asthma exacerbations. Although attractive, this hypothesis remains to be proven (14).

**Importance of human rhinovirus infections in childhood recurrent wheeze and asthma induction**

Associations between viral illnesses in early infancy and subsequent airway dysfunction and asthma have long been made. Infection with certain viruses, such as respiratory syncytial virus (RSV), has been shown to be an important risk factor for the subsequent development of asthma (4, 28). Other viral infections, especially HRV illnesses, also have been associated with recurrent wheezing illnesses and asthma; furthermore, the HRV-induced wheezing in infancy may be the first sign of childhood asthma (28, 33), and alternatively severe viral infections in early life may represent a marker of susceptible individuals (5). Early HRV wheezing illnesses are the most robust predictor of subsequent asthma development in high-risk children (34). Our previous studies also demonstrated that recurrent viral lower respiratory tract infections (LRTIs) in early age may predict the subsequent development of asthma, especially in atopic children (35). Hyvarinen et al. showed that the increased risk of asthma persists until the teenage years after hospitalization for wheezing in infancy. The risk was about 5-fold after respiratory syncytial virus-induced wheezing and more than 10-fold after rhinovirus-induced wheezing (36). Early childhood respiratory infections do not protect against asthma and atopic disease, as it was shown in 10-year follow-up of the Oslo birth cohort (37). The development of asthma may be a function...
of the “asthmagenic” pathogenicity of the strains of HRV causing asthma in infancy and of the efficacy of antiviral immune function at the time of infection. The protective effects of feeding a probiotic on the development of allergic disease might be due to enhancement of Th1-dependent mechanisms of antiviral defense, rather than a direct effect on mechanisms of allergic sensitization (38). By clarifying the roles of both host- (genetic) and virus- (environment) specific factors that contribute to the frequency and severity of viral LRTI, it may be possible to determine if severe LRTIs cause asthma, or if asthma susceptibility predisposes patients to severe LRTI in response to viral infection. Characterizing these relationships offers the potential of identifying at-risk hosts in whom preventing or delaying infection could alter the phenotypic expression of asthma (39, 40). Several lines of evidence indicate that most people diagnosed with asthma in the first two decades of life had recurrent episodes of wheezing in early childhood, suggesting that the disease process might have started years before diagnosis (41).

**New insights into key pathogenic mechanisms of human rhinovirus infections in asthma**

A lot of inflammatory factors could be released by HRV-infected airway epithelial cells. These mediators may induce the proliferation, chemotaxis, or activation of inflammatory cells (13, 42, 43). Wark et al. showed that bronchial epithelial cells of asthmatic subjects have an impaired apoptotic response to HRV infections and increased viral replication (44). This is caused by impairment of virus-induced type-1 interferon (IFN) expression. IFN may have an important role in recovery from HRV infections and in the prevention of virus-induced asthmatic exacerbations (31, 44). With the aim to identify a biomarker or biomarkers for acute virus-induced asthma, Wark et al. assessed the inflammatory mediators released from bronchial epithelial cells after infection with RV16. IFN-gamma-induced protein 10 (IP-10) serum level was increased, and IP-10 release was specific to acute virus-induced asthma and may be a predictor of viral trigger (45). Further studies are required to investigate the mechanisms of deficient IFN production in asthma and viral infection (46). Synthesis of cysteinyl-leukotrienes (cysLT) is increased in patients with asthma and viral wheeze (47).

Neutralizing antibodies to HRV infection in serum and secretions of patients is the most important for the antiviral mechanism of our adaptive immune system (27). Among infected volunteers, the detectable level of serum antibodies was observed between 1 and 2 weeks after inoculation. In initially antibody-free patients, serum antibodies could be detected only after 3 weeks. The highest levels of specific antibodies were determined after 5 weeks and persisted for at least 1 year (12). However, it is not clear whether B-cell responses to HRV infection are modified in patients suffering from asthma (31). It has been previously suggested that the degree of antibody-mediated protection from HRV infection is suboptimal in atopic subjects (27). The degree of the severity of asthma exacerbations was higher in children with high IgE levels. Differently to the specific antibody response, T cells showed the serotype cross-reactivity (12).

HRVs as the major trigger of acute asthma exacerbations are able to infect bronchial epithelium and induce production of proinflammatory, but also angiogenic and profibrotic mediators (48).

Induction of cellular IL-10 by viruses that target macrophages leads to suppression of the inflammatory response. IL-10 might be the “missing link” to explain the relationship between a viral respiratory infection and the provocation of an asthma exacerbation. As it was shown in the recent study by Grissell et al., IL-10 may be pointed as an indicator of HRV-induced asthma, both in children and adults (49).

Kirchberger et al. (12) hypothesize that the human and HRV relationship could be beneficial for humans due to viruses as a “training partner.” In persons with atopy, these “training sessions” may induce bronchial asthma. The presence of allergic inflammation seems to augment virus-induced inflammatory responses leading, especially after repetitive infections, to prolonged inflammation and airway hyperresponsiveness (AHR) and possibly to a more persistent asthma phenotype (5).

**Increased susceptibility to human rhinovirus infections in atopic asthma**

In some studies, novel mechanisms were identified due to increased susceptibility by showing that atopic adults with asthma have defective innate immune responses to HRV infection in vitro, which are related to markers of exacerbation severity in vivo (46). Respiratory viruses enter and replicate in epithelial cells lining the upper as well as the lower airways. Although HRV in particular was considered in the past as an upper respiratory pathogen only, studies using PCR and in situ hybridization have conclusively shown that HRV can also replicate in the lower airways. HRV serotypes 1b, 2, 7, 9, 14, 16, 41, and 70 were titrated in Ohio-HeLa cell cultures at either 33°C or 37°C (50). Viral infection induces greater nonspecific AHR in patients with respiratory allergy than
nonallergic controls, as it was shown using bronchial provocations with allergen after a viral infection (31). Papadopoulos et al. (31, 51) suggested that the defective epithelial repair cycle, characteristic of asthma and strongly correlating with AHR, is amplified by exposure to Th2 cytokines. The duration of postviral AHR after a single natural cold is around 7 weeks (5–11 weeks) in children with intermittent asthma. The cumulative prolongation of AHR is associated with an increased rate of cold and asthma episodes in atopic children. This opinion of Popadopoulos et al. (31) helps to explain the role of atopy as a risk factor for asthma persistence. Papadopoulos et al. in other paper (52) showed that infection of bronchial epithelial cells with RV1b and RV16 resulted in the production of a wide array of mediators that are able to chemotact eosinophils, such as eotaxin and eotaxin-2. These authors hypothesized that eosinophil recruitment after HRV infection of bronchial epithelium could represent a central event in the pathogenesis of virus-induced asthma exacerbations. The eosinophil infiltrate was more prolonged in asthmatic patients (6–8 weeks after infection), despite the fact that eosinophil infiltration was observed during cold in both asthmatic and non-asthmatic adults (31).

Synergism: virus infection and allergen exposure in sensitized asthmatics

Some studies have shown that sensitized allergic patients suffering from a viral infection have a very pronounced risk of developing a severe asthma worsening if they were concomitantly exposed to the relevant allergen. Synergistic effect of allergic sensitization, combined allergen exposure and viral infection increased almost 20-fold such a risk of hospitalization in sensitized children as well as over 8-fold in adults (31, 53, 54). Exposure of peripheral blood mononuclear cells (PBMCs) to RV16 and RV1b showed the suboptimal immune response to HRV in atopic asthmatic subjects, resulting in reduced viral clearance, increased viral proliferation, prolonged viral presence in the airways, and augmented virus-mediated cell damage, while a profibrotic, remodeling-associated response is promoted (55). It may be an important component of the inflammatory cascade that underlies asthma exacerbations (55) and the induction of airway remodeling.

Current options on the treatment and prevention of virus-induced asthma

Viral infections of the respiratory tract, as it was shown, are the most important triggers of asthma exacerbations and impact the treatment. Bush (56) concluded that the inhaled steroid therapy is rarely useful.

There are three potential methods of prevention or control of rhinoviruses: vaccines, antiviral agents (especially interferon), and interruption of transmission (57).

No efficacious vaccines yet exist for the prevention of RSV or HRV infections in humans. A variety of novel options for the prevention of virus-induced asthma need to be fully assessed for their efficacy and applicability (20).

Full protection against repeat infections with the same HRV serotype is given by serum neutralizing antibody, but cross-reactive antibody developed against other serotypes could yield a partial protection and result in attenuated cold and airway symptoms. Bardin proposed that vaccine-mediated induction of cross-reactive antibody might not prevent HRV infections but might reduce severe asthma symptoms and exacerbations (27). For example, although more than 100 different papilloma viruses are known to exist, a strategy using replication-defective particles produced a vaccine of high efficacy in clinical trials of cervical cancer (27). Experimental vaccines to certain HRV serotypes have been generated, but their usefulness is questionable because of the myriad serotypes and the uncertainty about mechanisms of immunity (58). Formalin-inactivated, parenterally administered vaccines induce antibodies in serum, but not in nasal secretions, and are not as useful as those given intranasally (57). A considerable interest exists in the development of vaccines against human RSV. Inactivated whole-virus vaccines have been ineffective (58). Monthly administration of RSV immunoglobulin (RSV Ig) or palivizumab has been approved as prophylaxis against human RSV for children aged less than 2 years who have bronchopulmonary dysplasia or cyanotic heart disease or who were born prematurely. Prophylactic topical intranasal application of interferon sprays has been effective in the prophylaxis of HRV infections, but is also associated with local irritation of the nasal mucosa (57, 58). Studies of the prevention of HRV infection by administration of antibodies to ICAM-1 or by the soluble purified receptors themselves have yielded disappointing results.

The recent study in vitro on the major and minor HRVs (RV9 and RV1b, respectively) demonstrated that fluticasone propionate and salmeterol may synergistically inhibit the production of angiogenic and/or profibrotic factors that are induced after RV infection of bronchial epithelial cells and are implicated in
Thorough hand washing, environmental decontamination, and protection against autoinoculation by minimizing finger-to-nose and hand-to-hand spread as well as by covering coughs and sneezes may help to reduce the rates of transmission of infection (57, 58).

The effective treatment and prevention of virus-induced asthma exacerbations recently is of great interest. The knowledge has increased substantially in the last few years. The first studies by Bisgaard et al. (PREVIA Study) (59) and Harmanči et al. (60) as well as the recent publications demonstrated that exacerbations of mild intermittent asthma in children aged 2–5 years could be successfully treated with leukotriene receptor antagonists (LTRAs) (61, 62). The recent study by Kearns et al. (63) showed that administration of montelukast for 7 days in 1- to 3-month-old infants with bronchiolitis and asthma-like symptoms was well tolerated as in pediatric patients aged between 3 and 24 months. During the annual peak in asthma exacerbations in September 2005 (September 1 to October 15), Johnston et al. recruited 194 asthmatic children aged 2–14 years to a double-blind, randomized, placebo-controlled trial of the addition of montelukast to usual asthma therapy with inhaled glucocorticoids (ICSs), either as monotherapy or in combination with long-acting beta-agonists (LABAs) (64). Children on montelukast experienced a 53% reduction in days with worse asthma symptoms as compared with placebo (P<0.02) and a 78% reduction in unscheduled physician visits for asthma (P<0.011). In the 12-month, multicenter, randomized, double-blind, placebo-controlled trial by Robertson et al. (SIMS Study), a short course of montelukast for at least 7 days, introduced at the first signs of an asthma episode or following each onset of upper respiratory tract infection in 220 children aged 2–14 years (80% were aged 2–5 years), resulted in a reliable reduction in asthma symptoms, acute health care resource utilization, school and parental work absence in children with intermittent asthma (65).

The recent PRACTALL consensus report on asthma in childhood recommends strategies that include phenotype-defining elements (virus-induced asthma, exercise-induced asthma, allergen-induced asthma, unresolved asthma) and pharmacological treatment. Leukotriene receptor antagonists are suggested as treatment for viral-induced wheeze and to reduce the frequency of exacerbations in young children aged 2–5 years (indication for asthma treatment in Lithuania is since 6 months of age) (66). In the recent task force of the European Respiratory Society, the large overlap in phenotypes was given, and the fact that patients can move from one phenotype to another, inhaled corticosteroids and montelukast may be considered on a trial basis in almost any preschool child with recurrent wheeze, but should be discontinued if there is no clear clinical benefit (67).

Conclusions

The current knowledge of the clinical significance of human rhinovirus infection in allergy and asthma development has increased in the last years. The contemporary opinion that rhinovirus infections contribute to the induction and development of asthma in atopic subjects was supported by original investigations. The combination of viral infection, allergen exposure, and allergic sensitization may be important for the synergistic effect and increased risk for asthma exacerbations and hospitalization. The treatment and prevention of virus-induced asthma exacerbations recently is of great interest. Future research needs to have a greater focus on the reduction of asthma exacerbations and health care costs.

**Žmogaus rinovirusai, alergija ir astma: klinikinis požiūris**

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**Raktažodžiai:** žmogaus rinovirusai, alergija, švokštimas, virusų sukelta astma, mechanizmai.

**Santrauka.** Alerginių ligų paplitimas didėja tiek Lietuvoje, tiek visame pasaulyje. Alerginės sensibilizacijos paplitimas – per 50 proc. populiacijos. „Higienos hipotezė“ teigia, kad dėl infekcijų poveikio sumažėja imuninė stimuliacija gali turėti įtakos didesniam atopenių ligų paplitimui. Tačiau, remiantis tik šia hipoteze, negalima tinkamai paaikinti akivaizdaus alerginių ligų paplitimo didėjimo. Žmogaus rinovirusinės infekcijos
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yra dažniausios infekcijos pasaulyje. Kvėpavimo takų virusinės infekcijos dažniausiai sukelia astmos paūmėjimus. Kadangi šiems paūmėjimams gydyti vaistai mažai veiksmingi, reikia naujo požiūrio į gydymą. Šios apžvalgos tikslas – pateikti naujausias žinias ir įvardinti klinikinę žmogaus rinovirusų reiškinę alergijos ir astmos raidai bei tolesnių tyrimų svarbą.

Naujausių tyrimų duomenys patvirtino, kad imuninis atsakas į žmogaus rinovirusus skiriasi tarp sergančiųjų astma ir sveikų asmenų. Pagal naujausią požiūrį į virusų sukeltos astmos paūmėjimų mechanizmus rinovirusinės infekcijos pažeidžia epitelio ląstelės, skatina uždegimą ir bronchų hiperreaktyvumą, taip pat profibročių atsaką ir kvėpavimo takų remodeliaciją. Naujausių tyrimų duomenimis, virusinės infekcijos sukelta imuninė stimuliacija skatina astmos pasireiškimą, tai atrodo įprastu infekcijomis žmogaus rinovirais ir anksčiau remdyti, tačiau jie nepasiklydo. Naujausi tyrimai rodo, kad rinovirusų infekcijos dažniausiai sukelia astmos paūmėjimus be reiškinės astmos, įprastu infekcijomis šiandien.
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