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■ Review article ■

Human rhinoviruses and asthma in children

Woo Kyung Kim, M.D.

Department of Pediatrics, Inje University, College of Medicine, Seoul, Korea

= Abstract =

Human rhinoviruses (HRVs) is a nonenveloped, single stranded RNA virus belonging to the family Picornavirudae. Transmission by direct contact such as hand-to-hand, hand-to-nose, and hand-to-eye has been readily demonstrated in experimental settings. HRV are the most frequent causes of common cold infection, however, they are also known to replicate in the lower respiratory tract and associated with more severe respiratory illnesses such as asthma. New technique such as reverse transcriptase polymerase chain reaction and molecular typing in HRV has been developed and our understanding of the importance of these respiratory viruses. HRVs consisted of 101 serotypes that are classified into groups A and B according to sequence variations. And there is a newly identified set of HRVs, called Group C, and it is currently under investigation. In recent study using PCR techniques, HRVs accounted for approximate 50-80% of common colds and 85 % of childhood asthma exacerbations and in more than half of adult exacerbations. However, the mechanisms of HRV- induced asthma exacerbations are poorly understood. This review discusses the association between HRVs and childhood asthma. (Korean J Pediatr 2010;53:129-135)

Key Words : Human rhinovirus, Asthma, Polymerase chain reaction

Introduction

Common colds are the most frequent infectious illness in humans. With from four to six colds per year in young children and two to four colds per year in adults, colds are an important cause of discomfort, occasional complications, and economic loss worldwide. Thus there are compelling reasons to understand the replication and pathogenesis of viruses that cause common colds[1, 2]. Early studies identified the principal viral etiologies of colds, notably Human rhinoviruses (HRVs) and coronaviruses, much progress was made in understanding the transmission, pathology, and clinical illness of common cold viruses. Subsequently, in the 1980s, more emphasis was placed on the structure, and replication of HRVs and coronaviruses[3-5]. Recently, the ability to define immune responses to common cold viruses has led to an increased understanding of the important role of host response during acute colds, as well as detailed understanding of the molecular biology and structure of HRVs[1, 6].

HRVs are well known for the causes of upper respiratory tract infections[7]. However, they can also results in acute otitis media[8, 9] and sinusitis[10, 11]. There is increasing evidence to support the role of HRV in lower airway infections. Recent studies have demonstrated the detection of HRV in the lower respiratory tract of children and adults and the effective replication of HRV in lower airway temperatures [12-14]. HRV is suspected to play a role in the inception of asthma early in life[13, 15]. Virus is the most common cause of infant bronchiolitis, which is associated with the development of childhood wheezing and asthma[13, 15]. However, it is not clear whether this association is "causal". The HRV is are a major cause of the common cold and the asthma exacerbation in children and adults[1, 12, 16]. This review highlights recent advances in our knowledge of HRV and the interaction between HRV and asthma.

Virologic features

HRV is a small nonenveloped, single stranded RNA virus (approximately 7.2 kb in length) belonging to the family Picornavirudae[1]. The first HRV was discovered in 1956[17, 18], and by the 1980s, 101 serotypes (A and B) were identified using cell cultures and specific anti-sera[19].

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Address for correspondence : Woo Kyung Kim, M.D., Ph.D.
Department of Pediatrics, Seoul-Paik Hospital, Inje University College of Medicine, 85, 2-ga, Jeo-dong, Jung-gu, Seoul, Korea 100-032
Tel; 82-2-2270-0057, Fax; 82-2-2270-0264
E-mail; ped3kim@yahoo.co.kr

The capsid is composed of four proteins (Fig. 1). Proteins VP1, VP2, and VP3 are on the surface of the viral capsid. Variations in these surface proteins are responsible for antigenic diversity and the host immune response following infection. VP4 is on the inside of the virus and anchors the RNA core to the viral capsid[20]. Following translation of the nonstructural and structural proteins, the viral RNA genome is replicated. HRV replication is an entirely cytoplasmic process. Replication of HRVs in the cytoplasm involves assembly of 60 subunits consisting of VP1, VP0, and VP3 into 12 pentamers. During the final maturation of the provirion particles, VP0 is cleaved to yield VP2 and VP4, resulting in infectious viral particles that are released from the cell by cell lysis. The entire life cycle requires from 5 to 10 hours[3, 21].

Pathogenesis

Transmission of HRVs has been studied in both experimental and natural conditions. Transmission by direct contact such as hand-to-hand, hand-to-nose, and hand-to-eye has been readily demonstrated in experimental settings. HRVs are relatively stable on environmental surfaces and on skin[1, 22, 23]. Certainly inoculation into the anterior nares is effective, and it is used as the route of experimental infection in volunteer studies. The peak of viral replication occurs from 24 to 48 hours after infection[24].

During initial viral replication in the nasopharyngeal epithelium, it does not appear that a large proportion of epithelial cells are infected, nor that there is significant demonstrated cytopathic effect in infected cells[24]. Viral replication increases for 2-3 days, as to be measured by titer of virus in nasal secretions. The duration of viral shedding is vary from several days to up to 28 days[25].

Infection of nasal epithelial cells results in increased neutrophils detectable in the nasal mucosa and secretions [26]. Inflammatory mediators are released following HRV infection are partially responsible for the common respiratory symptoms. The mediators are kinins, leukotrienes, interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α (TNF-α), RANTES (regulated upon activation normal T cell expressed and secreted), and etc[27, 28].

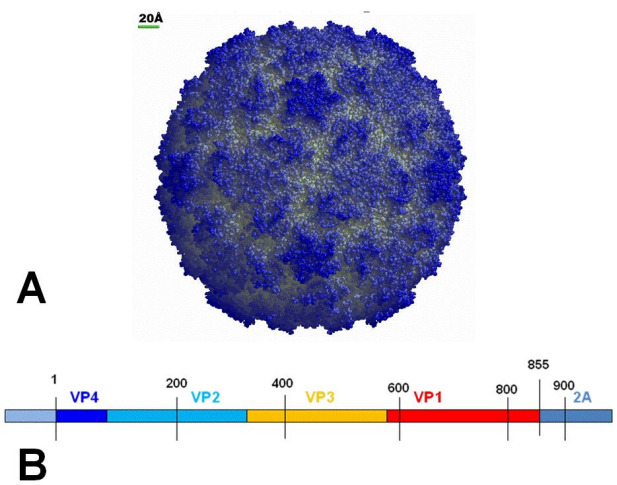

Fig. 1. Image of rhinovirus 16 (A), (Adapted form http://www.virology.wisc.edu/virusworld/ictv8/r16-human-rhinovirus-16-ictv8.jpg) and schematic of sequence analysis of the rhinovirus (B). VP4, VP2, VP3, VP1, and 2A (partial) are shown.

Diagnostics method

The rational diagnosis of viral diseases requires the identification of viral pathogens in clinical specimens and subsequent correlation between presence of the virus and the clinical syndrome.

Historically, standard viral detection techniques have relied on isolation and in vitro viral culture or immunological assays such as shell vials, direct fluorescence antibody, or enzyme immunoassay[29, 30]. More recently, the emergence of polymerase chain reaction (PCR) has revolutionized viral diagnostics by not only increasing detection sensitivity but also facilitating the detection of several viruses in parallel, either by multiplexing specific primers or through careful design of degenerate primers[14, 31, 32]. In diagnostic laboratories the use of PCR is limited by cost and sometimes the availability of adequate test sample volume. To overcome these shortcomings and to increase the diagnostic capacity of PCR, a variant termed multiplex PCR has been described. In multiplex PCR more than one target sequence can be amplified by including more than one pair of primers in the reaction. Multiplex PCR has the potential to produce considerable savings of time and effort within the laboratory without compromising test utility. Several other studies have found increased sensitivity of RT-PCR compared with viral culture techniques[31-34].

Molecular techniques of HRV were also used to find out the serotypes[35]. Briefly, a 260-bp variable region at the 5' noncoding region of HRV was amplified from the cDNA from specimens. The semi-nested PCR amplification fragment was cloned and sequenced. The identity of each sequence

was verified by comparing to the 5' sequences of the 101 reference HRV serotypes, as well as a number of sequences from newly identified strains[35-38]. Recent studies employing PCR and other molecular techniques indicate that there are new branches on the HRV family tree, and one characteristic of recently detected viruses is that they cannot be detected by standard tissue culture[35-38] (Fig. 2).

Epidemiology

In a study using PCR techniques, HRVs accounted for approximate 50-80% of common colds in studies. HRVs infect early childhood and into adulthood[35, 39]. HRV infections occur year round worldwide. In temperate climates, however, HRV infections are most prevalent in the fall (September and October) and spring (March and April)[40, 41]. Most HRV infections are symptomatic, so in respiratory infection such as HRVs are a frequent reason for inappropriate antibiotic use[42].

Association between HRV and asthma

HRV is the most common culprit in adults and older children, and respiratory syncytial virus (RSV) is the most frequent initiator in children younger than 2 years of age. Thus, both RV and RSV infections have been linked with asthma inception and exacerbation[43-45]. Viral infections can affect asthma in several different ways. First of all, in healthy infants, viruses such as RSV and parainfluenza can cause acute wheezing illnesses. In most infants these resolve with no sequelae related to lung health. However, in a subset of individuals chronic asthma can develop later on in childhood. Atopy appears to be a risk factor for the progression of recurrent wheezing in infancy to childhood asthma[43, 44]. Finally, viral infections can affect asthma disease activity in children or adults with established asthma. The viruses most commonly implicated are common cold viruses such as HRV. In individuals with asthma, HRV infections can cause exacerbations of asthma leading to hospitalization or utilization of emergency room facilities[13, 45, 46]. In animal models, enhanced lower airway responses to Sendai virus infection have been related to reduced IFN-γ production[47]. and data from a cohort of suburban infants (the Childhood Origins of Asthma [COAST] study) that will be utilized in the current proposal, suggest that reduced cytokine responses [e.g. IL-13] by cord blood mononuclear cells may also increase the risk for wheezing with RSV infection[48]. These findings provide evidence that immunologic responses that are established at the time of birth can affect the clinical expression of viral infections and wheezing illnesses in infancy. Children who develop wheezing with RSV infection are at an increased risk of recurrent wheezing and asthma in childhood[44, 48]. Interestingly, children who wheeze with HRVs or other non-RSV infections in infancy may be at even greater risk of asthma. These respiratory viral infections induce a broad array of cytokines, chemokines, and cellular inflammation into the airway. Th1 responses tend to predominate, leading to relatively high levels of interferon (IFN)-γ, and low levels of cytokines such as IL-4, IL-5, and IL-13. The risk of developing asthma after bronchiolitis in infancy is related to other signs or indicators of allergy, such as atopic dermatitis, food allergy, or allergic rhinitis[49, 50]. In addition, immunologic responses at the time of infection that are associated with recurrent wheezing after bronchiolitis include eosinophilic inflammation in airway secretions[51-53], reduced IFN-γ production from peripheral blood mononuclear cells (PBMC) ex vivo[54], and increased ex vivo PBMC IL-10 secretion during convalescence[55]. It is interesting that risk factors for asthma in infancy includees wheeze with viral infections, which induce Th1-like inflammation, and also development of Th2-like inflammation in the skin (atopic dermatitis), nose (allergic rhinitis), or gastrointestinal tract (food allergy). These findings suggest that the inability to control either Th1 or Th2-like inflammation confers the greatest risk for the development of asthma[56].

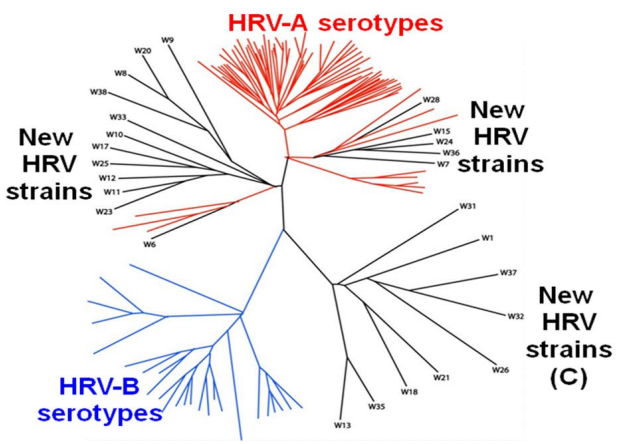

Fig. 2. Phylogenetic analysis shows 17 new strains belong to group A & 9 new strains form a new genetic group (C).

Asthma inception

Acute wheezing is predominantly related to viral respiratory infection. Most frequently, the first episode of asthma occurs in infancy; from a different perspective, infants who experience severe bronchiolitis have an increased chance to continue wheezing, at least throughout childhood. The debate whether the association between infection and reactive airway disease is causal is still active. RSV has long been considered as the major etiologic agent of acute bronchiolitis and its sequelae[43, 44]. Lately, however, HRV is particularly interesting, because it is the second most common virus, triggering early wheezing in as many as 45% of cases. Recently, rhinovirus induced early wheezing has been suggested as a new major risk factor, because it has been followed by third year wheezing in 65% of cases and school age asthma in 60% of cases[13, 45]. Further research will be necessary to find out the true relationship between the host (innate lung physiology) and viral factors in the diagnosis of asthma and the lung abnormalities.

Asthma exacerbations

Epidemiologic studies have detected viral infections in 85% of childhood asthma exacerbations[6] and in more than half of adult exacerbations; these upper respiratory infections are probably responsible for seasonal peaks of asthma related hospital admissions[46, 57, 58]. However, the mechanisms of HRV-induced asthma exacerbations are poorly understood. Lower respiratory illnesses are more likely to occur in specific high risk groups, including infants, and children and adults with asthma[12, 59]. In children and adults with established asthma, HRV infections can produce respiratory illnesses with a wide variety in severity, ranging from asymptomatic infection to common colds to severe exacerbations of asthma[59, 60].

The impacts of viral respiratory infections depend on the ability of the host to develop an appropriate protective response that clears the virus and to maintain normal airway structure[61]. The mechanisms by which HRV infections induce such exacerbations of lower airway diseases are not fully delineated, it is thought that infection of airway epithelial cells trigger epithelial responses that contribute to increased airway inflammation. In support of this, epithelial cells also leads to production of numerous proinflammatory cytokines and chemokines, including IL-1, IL-6, and IL-8, which correlate with the severity of respiratory symptoms during infection[62, 63].

To produce infection, HRVs must first attach first to specific cellular receptors embedded in the plasma membrane. Ninety percent of HRVs immunogenic variants use as receptor intercellular adhesion molecule-1 (ICAM-1) as a receptor, which is a cell surface glycoprotein that promotes intercellular signaling in processes derived from inflammation response[64, 65]. Recent reports indicate that the qualitative nature of this immuno-inflammatory response may be different in the asthmatic patients. These differences may include a reduced production of IL-12 and IFN-γ [56, 66], and a diminished production of antigen presenting cell surface markers after viral exposure[67]. These differences may explain, at least in part, why HRV infections more frequently involve in asthmatic patients, and why asthma symptoms in these persons are more severe and longer lasting[68]. IFNs are important antiviral proteins. The majority of these genes were associated with the IFN pathway, highlighting its significance in the host response to HRV infection[61].

Vascular endothelial growth factor (VEGF) is the major mediator of angiogenesis, an element of remodeling. HRV can induce proliferation and differentiation of endothelial cells, partly mediated by VEGF. These angiogenic responses could be important in the context of both the acute and chronic effects that result from HRV infection[69, 70].

CXCL8 and CXCL10, are also observed in increased amounts in airway secretions during in vivo HRV infections. Levels of both CXCL8 and CXCL10 correlate with symptom severity during HRV infections[71, 72]. CXCL8 is a potent chemoattractant for neutrophils, and neutrophil numbers in airway secretions have been shown to correlate with during viral exacerbations of asthma[73, 74]. CXCL10 is a chemoattractant for activated lymphocytes and natural killer cells that have been linked to host antiviral defenses.

Conclusion

There are a number of host factors that may make a host more susceptible to HRV infection, wheezing, and potentially asthma. There have been specific polymorphisms associated with viral wheezing. In addition a number of groups have demonstrated that asthmatic individuals may have more severe HRV infections secondary to impaired

INF responses. The abnormalities in lung physiology have been demonstrated in children susceptible to early childhood wheezing and it is the most prevalent human pathogen and different strains of HRV may cause a range of respiratory illnesses. Finally, there is a newly identified set of HRVs, called Group C, which is currently under investigation whether this group or other strains of HRV may be particularly pathogenic.

Ultimately, I suggest that it is a combination of these host factors and virus factors that lead to the clear relationship of early childhood wheezing with HRV and the subsequent development of asthma.

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