New Aspects on Human Rhinovirus Infections

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Many large studies performed in 1960s detected human rhinovirus (HRV) by virus isolation in one quarter of the cases with acute upper respiratory infections, and HRV was mainly considered a common cold virus. Virus culture, the standard method for detection, was carried out in research laboratories with special expertise and the role of HRV outside common cold remained unclear. During 1990s, polymerase chain reaction (PCR) techniques for HRV became generally available and they revolutionized HRV studies bringing important new biologic and clinical observations.1–3

Virology

HRVs are positive-strand RNA viruses of the genus Enterovirus in the family Picornaviridae. In addition to HRV, enterovirus, parechovirus and hepatovirus in the picornavirus family cause human infections. With virus culture techniques 100 HRV serotypes have been identified. Genome sequencing revealed originally 2 species, A and B. Recent studies of strains, which were uncultivable but detectable by PCR, resulted in classification of new species C with a current number of 60 genotypes. They also show that recombinatorial events have taken place during the evolution of HRVs. HRV-C viruses do not use intercellular adhesion molecule-1 (major) or the low-density lipoprotein receptor (minor) as receptors as do HRV-A and HRV-B species.4–7

Clinical Profile on Natural Rhinovirus Infections

HRV is undoubtedly the most commonly detected respiratory virus in all age groups and probably the most common causative agent of all acute infections in humans. By 2 years of age, >90% of the children have experienced at least 1 HRV infection.4 HRVs are associated with 5 hospitalizations per 1000 children <5 years old in the United States.8 HRV infection is associated with a wide range of clinical presentations including classic common cold, acute otitis media (AOM), sinusitis, severe bronchiolitis, asthma, pneumonia, fever alone, infections in preterm infants, severe infections in immunosuppressed patients, as well as worsening of chronic conditions particularly asthma, cystic fibrosis and chronic obstructive pulmonary disease. It is becoming well established that HRV-A and HRV-C are more common and may cause more severe illnesses in infants than HRV-B.7 PCR studies also suggest that subclinical infections may be much more common than earlier understood. Subclinical infections have also been recorded many years ago in experimental HRV studies, in which virus culture was used.10

Common Cold

Compared with other respiratory viruses, HRVs have a dominant role as causative agents of upper respiratory tract infections both in young children, adults and elderly people. HRVs were detected in 52% of 200 young adults with common cold and in 92% during September and October.11 In 194 young children with newly onset common cold at least 1 respiratory virus was detected in 92% of the patients. HRV was the most common respiratory virus, found in 71% of the children.12

Acute Otitis Media

Respiratory syncytial virus (RSV) has earlier been considered a major predisposing factor to development of AOM. Studies with HRV PCR suggest a dominant role of also HRVs.13 In the Finnish Otitis Media Cohort Study, 759 AOM events were recorded and 42% of these events were associated with HRV infections. In the second part of this study, HRV was detected in 32% of 1416 AOM events. Rhinovirus RNA has been detected in 17%–41% of the middle ear fluid specimens from children with AOM.14

Bronchiolitis, Recurrent Wheezing and Asthma

HRV is associated in up to one quarter of bronchiolitis cases in infants. In a 3-year prospective study, Calvo and colleagues15 investigated the frequency of 16 respiratory viruses in 318 children (mean age 6 months) hospitalized with bronchiolitis. A virus was found in 87% of the cases, RSV in 61% and HRV in 17%. In a prospective multicenter 3-year study in the United States, Mansbach and colleagues examined 2207 children younger than 2 years hospitalized for severe bronchiolitis. A virus was detected in 94% of the cases, RSV in 72% and HRV in 26%, and other viruses in 7%.16 RSV dominates in infants and HRV in children older than 12 months.17 Interestingly, HRV-infected children had a significantly shorter hospital...
length of stay as compared with children with RSV bronchiolitis. Fatal HRV bronchiolitis was recently reported in Vietnam. In late immune responses inversely correlate with the HRV disease severity.

Several studies have shown that infants with bronchiolitis will have significantly more often recurrent wheezing than controls without bronchiolitis. HRV as the causative agent is the most important risk factor, followed by a positive family history for asthma or atopy. Severe episodes of bronchiolitis increase the odds of early asthma.21 In a long-term postbronchiolitis follow-up in Finland, asthma at 7 years of age was more common after HRV (52%) than after RSV (15%) bronchiolitis.20 At the moment it is not understood whether HRV infection causes asthma or whether it only identifies the susceptible children and promotes the development. There is evidence that early prednisolone treatment of HRV-induced wheezing may reduce recurrent wheezing. This requires further confirmation, as prednisolone treatment does not achieve a similar benefit in bronchiolitis caused by RSV.24

Up to 90% of asthma exacerbations in children are associated with virologically defined natural respiratory virus infections. HRV is the most commonly found virus and is detected approximately in two thirds of the cases. Children with asthma and allergic sensitization are more prone to HRV infections. There is evidence that asthmatic patients have more frequent HRV, more severe, and longer lasting lower respiratory tract infections than nonasthmatics. Many studies have unveiled the mechanisms of increased susceptibility to HRV infections in asthmatic patients. They include changes in airway epithelium, defective HRV-induced secretion of interferon-β, interferon-λ, interleukin-10 and probably interferon-γ, and impaired alveolar macrophage function.

**Pneumonia**

HRV has been indentified from induced sputum, tracheal brushing, bronchoalveolar lavage samples and lung tissue samples strongly suggesting that HRV can induce lower respiratory tract infections. Nine studies on childhood community-acquired pneumonia (CAP) (N = 4279 episodes) using PCR methods for virus detection found HRV in 18% of the cases.29 In 1 new study in Italy, 592 children with CAP were included and HRV was identified in 172 cases (29%).77 The clinical profile of 643 HRV infections in children admitted to hospital were reported in 7 studies and 11%–53% had pneumonia.26,28 HRVs are commonly detected in children with severe pneumonia also in developing countries. These new findings suggest that HRVs are important causative agents of pneumonia both in children and in adults and in immunosuppressed subjects.

**HRV RNA in Asymptomatic Individuals**

The clinical importance of detection HRV RNA by RT-PCR can be questioned. HRV RNA can be detected before, during and after symptomatic infection, in subclinical infection, or it may just be an innocent contamination. Several studies have indentified HRV RNA in 12%–35% of asymtomatic subjects. In 1 recent study, HRV was detected in the nasopharynx of 433 6- to 24-month-old healthy children from 31% to 50% of samples. It is important to recognize that in otherwise healthy subjects, HRV is not known to induce chronic illness and virus shedding lasts 2–4 weeks after acute HRV infection. For these reasons, Jartti and coworkers25 concluded that PCR-positive respiratory HRV finding detects most probably true infection with or without symptoms.

**Coinfections With Other Viruses and Bacteria**

In 4 recent studies, HRV was detected in association with one or more other respiratory viruses in 24%, 34%, 37% and 70% of the cases.2,12,15,16,34 The clinical relevance of detection of several viruses is uncertain and it certainly can be asked what is the role of HRV when it is detected by PCR with 3 other viruses.

Interest has grown with respect to the interaction of bacteria and viruses in the pathogenesis of respiratory infections. Earlier, in contrast to for example influenza viruses, HRVs have not been considered to facilitate bacterial coinfections. Ruohola and coworkers studied etiology of AOM in 79 middle ear fluids suctioned through tympanostomy tube. In 16 cases HRV was detected, and in all cases they were detected together with pathogenic bacteria.13 Honkinnen and colleagues29 studied induced sputum of 76 children with CAP and found HRV plus *Streptococcus pneumoniae* in 12 of 23 HRV cases. Similarly, in adults with CAP the most frequent viral–bacterial combination has been HRV plus *S. pneumoniae*.32 Peltola and coworkers13 found a temporal association between HRV infection and invasive pneumococcal disease in children.

Experimental HRV infection in patients with chronic obstructive pulmonary disease was followed by secondary bacterial infection in 60% of the subjects. Bacterial infections were associated with reduced levels of antimicrobial peptides.34 In healthy children, *S. pneumoniae* was positively associated with HRV in the nasopharynx.31 New observations in mice suggest that HRV may increase the risk of secondary bacterial infec- tion by attenuating TLR-dependent immune responses.

**Diagnosis**

Today RT-PCR is the method of choice for the detection of HRV because it is easier to perform, more sensitive than HRV culture and detects HRV-C. However, it should be emphasized, that a positive PCR test result does not necessarily reflect active virus replication, as does positive virus culture. A difficulty with HRV is the paucity of serologic tests to verify acute infection.

Including HRV into multiplex PCR assays has increased the number of diagnoses. The most sensitive PCRs for HRVs amplify parts of the 5' noncoding region. They are not always selective for HRVs but also detect human enteroviruses. The differentiation requires additional confirmation like sequencing, although melting temperature determination can be used as a screening tool.33 Flocked swabs with nylon fibres are now preferred for nasal or nasopharyngeal sampling because they are convenient to use and have similar or better sensitivity than nasopharyngeal aspirates or nasopharyngeal cultures.36 Self sampling conducted at home by the parents with subsequent shipping of the samples by mail to the laboratory has been successfully used in clinical studies.36

The clinical significance of HRV load is not well established. Jansen and coworkers30 detected higher HRV loads in children with acute symptomatic respiratory infections compared with asymptomatic controls. Utokaparch and associates30 detected significantly higher HRV load in lower respiratory tract infections versus nonlower respiratory tract infections. On the other hand, no correlation between HRV load and the disease severity was reported by Takeyama et al.41

**Treatment and Prevention**

No antiviral drug has been approved for clinical use in HRV infections. All possible candidates have turned out to be disappointments. Oral capsid-binding HRV inhibitor, vapendavir and inhaled interferon-β are being studied.35 New HRV marine models may facilitate the development of new agents.41

The antigenic diversity of HRV makes development of effective vaccines difficult. At the moment, the only way to reduce HRV disease burden is prevention of transmission. In a family setting, the rates of HRV infections were 1.00 cases per person among siblings and 0.50 cases per person among parents of HRV-positive index patients.36 Studies carried out 15–25 years ago showed that a major route of transmission is probably from hands of infected subjects to an intermediate surface or directly to the fingers of the susceptible recipient. HRV may remain...
infectious for at least several hours on different surfaces like doorknobs, refrigerator door handles and television remote controls.\textsuperscript{43} Infection is then transmitted by self-inoculation of the nose or eye. Importantly, this chain may be effectively interrupted by the old technique—washing hands with water and soap, which removes HRV efficiently.\textsuperscript{44} However, hand disinfection with 2% citric acid and 2% malic acid in 62% ethanol does not reduce HRV infection or HRV-related common cold illnesses.\textsuperscript{46}

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