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Clinical effects of rhinovirus infections

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ABSTRACT

Rhinovirus is the major cause of common cold and frequently associates with acute wheezing, otitis media, sinusitis, and pneumonia. High prevalence of rhinovirus in hospitalized children and adults has been documented recently. We screened children ≥1 month of age, hospitalized for any infection, for the presence of rhinoviruses and recruited 24 families with ≥2 children for a 3-week follow-up study. Rhinovirus was detected in 46 (28%) of 163 hospitalizations by study children. Most rhinovirus-positive children (85%) had respiratory symptoms. During the follow-up, rhinoviruses were detected in virtually all children and in one-half of adults in families with a rhinovirus-positive index child, but commonly also in families with a rhinovirus-negative index child. Melting temperature and sequence analysis revealed the transmission routes of the viruses and showed that several virus types could circulate in the families simultaneously. Our studies corroborate the major contribution of rhinovirus to hospitalization of children, most often because of wheezing. Young children with respiratory symptoms are major spreaders of rhinovirus in family setting.

1. Introduction

Rhinovirus was first isolated in 1956 and, during next decades, several large studies established it as "the common cold virus". Rhinovirus was cultured in one-quarter of upper respiratory tract specimens taken from people with common cold, but notably, only in less than 5% of those with no respiratory symptoms.[1–3] Development of sensitive and specific reverse transcription (RT) PCR methods has markedly increased the detection rate of rhinovirus. In addition to upper respiratory tract infection, rhinovirus has been often detected by RT-PCR also in children and adults with more severe diseases. Clinical manifestations of rhinovirus infection in previously healthy individuals range from asymptomatic state to common cold, wheezing illnesses, and pneumonia. Viral–bacterial interaction is often involved in development of rhinovirus-associated otitis media, sinusitis, or pneumonia. Life-threatening and chronic rhinoviral infections may occur in immunocompromised individuals. However, not many institutions have adopted rhinovirus diagnostics in routine clinical use, and we still know much less about the clinical impact of rhinovirus compared with viruses such as influenza A and B, or respiratory syncytial virus (RSV). Because effective vaccines and antivirals are not available, intervention studies aiming to show decrease in disease burden by specifically targeting rhinovirus are presently not possible.

2. Burden of rhinovirus infections in the community

By using both RT-PCR and culture, rhinovirus has been documented to cause one-half of common cold cases in adults year-around.[4] Several rhinovirus types circulate in the community throughout the year, but peaks of high prevalence occur usually in September–November and April–May.[5,6] During autumn season up to 90% of colds in adults are caused by rhinovirus.[4,7] Similarly to adult people, rhinovirus is the most common agent causing respiratory tract infections in children in the community.[5,8,9]

Community impact of rhinovirus infections is seen as visits to primary health-care providers, use of prescription and non-prescription medications, and sick leaves of adults from work and children from school or day care. Young children often need a parent to take care of them at home, causing additional absences of parents from their workplaces. A substantial proportion of all antibiotic use is directed to documented or suspected bacterial complications of common cold. Symptomatic cold remedies are highly used despite their limited efficiency.

In the USA, 500 million non-influenza viral respiratory infections have been estimated to occur annually, resulting in 40 billion

Abbreviations: RT-PCR, reverse transcription PCR; RSV, respiratory syncytial virus; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

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US dollar direct and indirect costs.[10] In an Australian cohort of pre-school aged children followed by a diary and parent-collected specimens for viral detection, the mean cost of a respiratory picornavirus (rhinovirus or enterovirus) illness was 267 Australian dollars (154 €) and picornaviruses were associated with the highest overall costs during the study, compared with other respiratory viruses.[11]

Otitis media accounts for a substantial proportion of the disease burden in children caused by rhinovirus. In a cohort study following children from 2 months to 2 years of age, rhinovirus was detected in nasopharyngeal sample in 40% of acute otitis media episodes.[12] Most cases of rhinovirus-associated otitis are viral–bacterial co-infections. Both viruses and bacteria were found in two-thirds of middle ear fluid aspirates taken from children with acute otorrhea through a tympanostomy tube, and rhinovirus was the most common viral finding.[13] *Streptococcus pneumoniae* is the most common bacterial cause of otitis media. Conjugated pneumococcal vaccines have been recently included in childhood immunization programs of many countries, but they have only limited effect on otitis media. A better strategy might be development of a rhinoviral vaccine, which would prevent otitis by attacking the first step in viral–bacterial pathogenic process.

3. Rhinovirus in hospitalized patients

In a population-based study from the USA, children <5 years of age admitted to five surveillance hospitals with acute respiratory symptoms or fever during a 1-year period were tested for rhinovirus and other respiratory viruses by RT-PCR and culture.[14] Rhinovirus was detected in 26%, RSV in 20%, influenza A or B in 3%, and other virus in 12% of children. Rhinovirus-associated hospitalization rate was calculated as 4.8/1000 children <5 years of age/year (95% confidence interval [CI], 4.3–5.2). Hospitalization rate was highest in the youngest infants (17.6/1000 children 0–5 months of age; 95% CI, 14.9–20.6). Similarly, in a study from Hong Kong, rhinovirus was the most commonly detected virus in children hospitalized with an acute respiratory infection.[15] Among children <2 years of age hospitalized in Spain with a respiratory tract infection, rhinovirus was the second most common virus after RSV.[16]

We studied prospectively rhinovirus, enteroviruses, and RSV in children admitted to the Pediatric Infectious Disease Ward, Turku University Hospital (Peltola et al., unpublished). During a 2-month period in autumn, nasal swab sample was taken for semiquantitative multiplex RT-PCR for rhinovirus, enteroviruses and RSV from all children ≥1 month of age regardless of presenting symptoms. Rhinovirus was detected in 46 (28%) of 163 hospitalizations by study children, whereas enteroviruses were detected in 22 (13%), and RSV in 20 episodes (12%). The median age of children with rhinovirus infection was 1.7 years (interquartile range, 0.7–3.4 years). Viral copy numbers were highest in children younger than 2 years of age. Respiratory symptoms were present on the day of nasal swab sampling in 85% of children with rhinovirus infection, and in all children with enterovirus or RSV infection. An acute wheezing illness was diagnosed in 28 (61%) of the 46 children with a rhinovirus infection and in 36 (31%) of the 117 children with another study virus, or no study virus detected ($P < .001$, χ^2-test).

Our study corroborates the major contribution of rhinovirus to hospitalization of children, often because of wheezing. Other studies have strongly associated acute wheezing (asthma exacerbation or bronchiolitis) with rhinovirus in infants, older children, and adults.[8,14,17–19] Rhinovirus-induced wheezing in infancy carries a higher risk of development of asthma than wheezing associated with other viruses,[20,21] and this association remains until adulthood.[22]

Rhinovirus has been documented frequently in adults hospitalized because of acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD),[23,24] severe lower respiratory tract infections in immunocompromised patients,[25] or cardiopulmonary illnesses.[26] The full impact of rhinovirus in hospitalizations of adults is still unknown as large population-based studies are lacking.

4. Pneumonia

Firm etiologic diagnosis of pneumonia is difficult to reach in clinical practice, because sampling from the lungs is unfeasible. Experimental studies and clinical studies with small numbers of selected patients show that rhinovirus can replicate in lower respiratory tract.[27–30] Rhinovirus can be detected in 24–45% of children[31,32] and in 10–18% of adults with pneumonia in upper respiratory or sputum samples.[33,34] However, as rhinoviruses are commonly detected from subjects with mild respiratory symptoms, and even from asymptomatic individuals, the causative role of rhinovirus detected in the upper airways remains controversial. In our study of rhinovirus, enteroviruses, and RSV in children admitted to the Pediatric Infectious Disease Ward, pneumonia was not as common in children with rhinovirus as in those with other study virus or no virus (Peltola et al., unpublished). More studies with carefully selected comparison groups are needed to define the role of rhinovirus in pneumonia.

Rhinovirus is often found together with *S. pneumoniae* or other pathogenic bacteria in patients with pneumonia. Viral–bacterial pneumonia has a poorer response to treatment than that caused by a single agent.[33–35] Few studies have addressed the pathogenesis of mixed rhinoviral–bacterial infection. Rhinovirus infection of epithelial cells has been shown to increase adherence of pneumococcus,[36] and rhinovirus impairs immune response of macrophages to bacterial lipopolysaccharide and lipoteichoic acid.[37] Other mechanisms likely also play a role in the development of secondary bacterial pneumonia during or after rhinovirus infection.

5. Molecular epidemiology

Partial genome sequencing is an effective tool for identification of rhinovirus types.[38] Molecular epidemiology studies extend earlier findings from viral culture and serotyping, which documented that several rhinovirus types circulate in the community simultaneously.[39] Genetic diversity of rhinoviruses circulating in a community cohort of young children during 2 years of follow-up was remarkably wide.[40] An entirely new genetic group of human rhinoviruses has been recently identified by sequencing.[41–45] Attempts to grow these group C human rhinoviruses in cell lines commonly used for rhinovirus culture have so far been unsuccessful.

We have used sequence analysis of 5′-noncoding region and VP1 region in typing of rhinoviruses. The 5′-noncoding region is well suited for specific identification and differentiation of entero- and rhinoviruses,[46,47] and sequence variation in this region can be used in differentiation between rhinovirus genotypes in epidemiologic studies. VP1 is an antigenic region where genetic variability better associates with the serotypes.[48,49] Sequencing of 5′-noncoding region can be done directly from the RT-PCR product generated from viral RNA from clinical specimen. Melting temperature can be used in preliminary differentiation between virus groups before sequence analysis.

We have shown that nasal swab samples can be self-collected at home and returned to the laboratory by mail without a substan-

tial loss in sensitivity for virus detection.[50] In this way repeated samples for transmission and circulation studies can be received efficiently. We screened hospitalized children for rhinoviruses, and followed-up 24 families with either rhinovirus-positive or rhinovirus-negative index child for 3 weeks by twice-weekly nasal swab samples and a diary for disease symptoms in all household members.[51] Rhinoviruses were detected in virtually all children and in one-half of adults in families with a rhinovirus-positive child. Symptomatic infections were associated with age <7 years (cumulative odds ratio 14.3, 95% CI 3.9–52.3, $P = 0.0005$). Rhinoviruses were commonly detected also in comparison families with a rhinovirus-negative child. These findings suggest that rhinoviruses are easily transmitted from young children to other household members, but adolescents and adults are often protected from development of symptomatic infection. Sequencing of viruses showed that even during short follow-up of 3 weeks, several rhinovirus types occurred in members of same household, and also in individual subjects. This finding highlights the advantages of molecular typing methods in transmission and circulation studies. If rhinovirus is detected repeatedly from same individual, documentation of same virus type from all specimens is essential before a chronic or long-term infection can be reported.

6. Rhinovirus in asymptomatic individuals

Rhinovirus has been detected by RT-PCR in average from 15% of asymptomatic individuals, compared with <5% for most other respiratory viruses.[52] Besides technical false positive, rhinovirus in asymptomatic subject could represent (1) symptomatic infection with unrecognized, mild symptoms, (2) incubation period before development of symptoms, (3) remaining viral genetic material after symptomatic infection, or (4) truly asymptomatic infection. Data reviewed by Jartti et al.[52] supports that each one of these possibilities explains part of asymptomatic cases. Our family follow-up study suggests that truly asymptomatic infections are common at least in families with children.[51] Detection of rhinovirus from asymptomatic individual was not associated with symptoms before or after sample collection. Instead, asymptomatic virus detection was significantly associated with simultaneous symptomatic infection in other household members. Asymptomatic infections were of short duration, usually less than 1 week. In parallel with these results, detection of same rhinovirus strains 2 or more weeks apart from infants with recurrent respiratory infections was rare in another recent study.[53] Chronic rhinovirus infection has been reliably documented only in immunocompromised subjects.[27]

7. Conclusions

Although recognized for decades as the major cause of common cold, the multiple roles of rhinovirus in respiratory infections of children and adults have been investigated more thoroughly only recently. Molecular detection and typing methods have been used to document rhinovirus as the most prevalent agent associated with acute wheezing, otitis media, and hospitalization with respiratory infection of children, and as an important cause of severe pneumonia and exacerbation of asthma or COPD in adults. Young children with respiratory symptoms have a major role in transmission of rhinovirus. Several other clinical effects of rhinovirus are still controversial or poorly reported. Possible differences in clinical associations between rhinovirus types are not known. Almost all clinical studies on rhinovirus infections have been conducted in developed countries. The effect of rhinovirus on morbidity and mortality in developing countries is unknown, but it can be anticipated to be high.[54] Considering the frequency and severity of rhinovirus infections, the lack of prevention and treatment modalities is alarming and their development should be given a high priority.

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