Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia

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Abstract

The shedding of human rhinovirus (HRV) after an acute, naturally acquired infection has not been described in detail. We determined the duration of HRV shedding in immunocompetent children and adults, and in patients with primary hypogammaglobulinaemia. Subjects with symptoms of respiratory tract infection, and their household contacts, were screened for HRV by reverse transcription PCR. They were followed by serial, self-collected nasal swab specimens until negative for HRV or infected by another HRV type. We followed 62 HRV infections in 54 subjects. The mean (95% CI) duration of HRV shedding was 11.4 (8.2–14.7) days in children, 10.1 (7.4–12.9) days in adults, and 40.9 (26.4–55.4) days in patients with hypogammaglobulinaemia ($p < 0.001$). The duration of respiratory tract symptoms correlated with the duration of virus shedding (p 0.002). A new infection by another HRV type soon after the first episode was common. We conclude that the shedding times of HRV are relatively short in otherwise healthy individuals. In contrast, prolonged shedding over 28 days is frequent in patients with hypogammaglobulinaemia despite immunoglobulin replacement therapy.

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Introduction

Human rhinovirus (HRV) is the most frequent of all agents that cause respiratory tract infections in children and adults. The common cold, exacerbation of chronic obstructive pulmonary disease, wheezing illnesses (bronchiolitis, recurrent wheezing and asthma exacerbation), viral pneumonia and viral–bacterial co-infections are typical clinical manifestations of HRV infection [1–8].

Human rhinovirus is a single-stranded RNA virus that multiplies in the respiratory tract. The duration of HRV shedding in healthy people, or in those with chronic conditions, is not well characterized. A long period of shedding, or carriage of the virus, has been suggested based on the fact that HRV can be detected by RT-PCR in 15% of asymptomatic children (combined prevalence data from several studies, range up to 45%) [9,10]. However, HRV has been documented to cause chronic infections only in patients with immunodeficiency due to primary hypogammaglobulinaemia or organ transplantation [11–13]. Several HRV types can circulate simultaneously, which makes it difficult to separate sequential infections by different HRV types from each other if virus typing is not performed [14,15]. The shedding times of HRV after an acute infection would be needed to clarify the clinical significance of HRV detection in healthy and immunocompromised individuals, to optimize infection control measures, and to study the pathogenesis of HRV infection.

The current standard method in laboratory diagnosis of HRV infection is RT-PCR analysis of conservative regions of the HRV genome. More than 150 HRV types of species A, B and C can be detected by RT-PCR, but the routine methods do not allow typing of HRV. This can be done by sequencing of genomic regions coding for the capsid proteins of the virus, VP1 and/or VP2/4. Sequence analysis of the hypervariable non-coding region of the genome and differences in the melting temperatures of the PCR products have also been

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used successfully for differentiation of viruses in molecular epidemiological studies [14]. The high-resolution melt (HRM) method allows comparison of two or more specimens after a single PCR without the need for second amplification for sequencing. Weakly positive specimens produce clear melting temperature (T_m) values more often than an unambiguous sequence. On the other hand, different strains may have identical T_m (but not vice versa). Depending on the genomic target, sequencing gives species and type information not obtained by the HRM analysis.

Here, we report the duration of HRV shedding in immunocompetent children and adults, and, as a comparison, in hypogammaglobulinaemic patients after an acute respiratory tract infection with HRV. Sequential infections caused by different HRV types were identified and distinguished from the shedding of the primarily detected virus.

Methods

Study population and design

Study subjects were immunocompetent children and adults, and patients with hypogammaglobulinaemia. Children were recruited to the study at the time of hospitalization at the Department of Paediatrics, Turku University Hospital, between July and November 2010, with a respiratory tract infection. Family members (children and adults) of hospitalized children and hospital personnel were also recruited to the study. With the exception of hypogammaglobulinaemia, we excluded people with other severe chronic conditions; asthma was not considered a severe chronic condition. The patient group with hypogammaglobulinaemia comprised 12 patients with common variable immunodeficiency and one with X-linked agammaglobulinaemia. Two patients were receiving subcutaneous and 11 were receiving intravenous immunoglobulin replacement therapy. The trough serum IgG concentration was >6.5 g/L in all patients. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol. Participants, or parents of participating children, gave their written, informed consent.

Subjects were screened for HRV by RT-PCR in nasal swabs when they or their household contacts developed symptoms of the common cold. Those who were positive for HRV, or parents of children, were instructed to self-collect nasal swab samples at least twice per week by using flocked swabs (Copan, Brescia, Italy) and send samples to the laboratory by mail, as described earlier [14]. Collection of samples was continued until two negative samples were obtained, or longer if the subject developed new respiratory symptoms. Participants (or parents of children) recorded the existence and severity of respiratory symptoms (nasal discharge and stuffiness, cough and sore throat) and fever daily in a diary. Duration of the virus shedding was calculated from the onset of symptoms until the last sample positive for the same HRV type. In a few cases, the onset of symptoms was unclear and the duration of shedding was calculated from the first positive to the last positive sample. Duration of symptoms was calculated from the first day when any above-mentioned symptoms were recorded until the last day with any such symptoms.

In addition to providing new data on HRV infections in hypogammaglobulinaemic patients, we re-analysed our earlier results in patients with this disorder and calculated the duration of episodes of HRV. We previously followed respiratory virus infections in a group of nine hypogammaglobulinaemic patients who included four of the participants with hypogammaglobulinaemia in the present study, by using self-collection of nasal cotton swab samples with 2-week intervals and similar RT-PCR methods for HRV [12].

Human rhinovirus detection

Screening of the specimens was performed by RT-PCR as described previously [14,16]. Briefly, mucus in the nasal swab was suspended into phosphate-buffered saline and nucleic acids were extracted using easyMag extractor (BioMérieux, Marcy l'Etoile, France). Reverse transcription and PCR were performed using primers specific to the 5′ non-coding region of human picornaviruses. Detection of HRV was confirmed using proprietary probes differentiating between rhinoviruses and enteroviruses. When all specimens from the same individual were screened, the corresponding cDNAs, stored at −70°C, were analysed in a single PCR run using HRM analysis for the T_m determination of the product (see Supplementary material: Supporting HRM Information and Fig. S1).

Statistical analysis

Duration of HRV shedding was estimated using the Kaplan–Meier method and compared among children, adults and patients with hypogammaglobulinaemia by using the Log-rank test. Chi-square or Fisher's test was used to compare predefined subgroups of healthy children and adults. The correlation between the duration of respiratory tract symptoms and duration of virus shedding was analysed using the Pearson correlation coefficient. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were carried out using the SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

We detected HRV by RT-PCR in 55 of 74 subjects screened. Fifty complied with the follow up by serial self-collected nasal

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