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Comparison of Human Metapneumovirus, Respiratory Syncytial Virus and Rhinovirus Respiratory Tract Infections in Young Children Admitted to Hospital

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Respiratory Syncytial Virus (RSV), *Human metapneumovirus* (HMPV), and *Rhinoviruses* (RV) are frequent causes of respiratory tract infections in young children. We compared laboratory and clinical findings in children with comparable age distribution and hospitalized due to RSV, HMPV or RV infections. Viral pathogens were detected by a quantitative real time PCR from nasopharyngeal aspirates. No significant differences in the admission diagnosis, laboratory parameters, patient demographics and treatment measures between the three viral causes of respiratory illness were found. No correlation between viral load and disease severity was observed however, there was a significantly lower concentration of the nasopharyngeal interleukin 8 (IL-8) in children with RV compared to HMPV and RSV, indicating a milder proinflammatory reaction. Moreover, RV-infected children had significantly lower body temperature, higher leucocyte counts in peripheral blood, and a tendency to have a shorter stay in hospital than children with either HMPV or RSV infection. Taken together, clinical presentation of the infections with RSV, HMPV, and RV is similar among children of the same age group and not clearly distinguishable by standard clinical or laboratory findings. Therefore, virus specific testing should be included regularly for routine diagnosis of children with respiratory tract infections. ***J. Med. Virol. 87:275–280, 2015.***

KEY WORDS: HMPV; RSV; RV; real-time-PCR

INTRODUCTION

Respiratory syncytial virus (RSV) and *Human metapneumovirus* (HMPV) are important causes of upper and lower respiratory tract infections and hospitalization in young children worldwide. Additionally, recent studies suggest that *rhinoviruses* also play a major role as a cause of respiratory tract infections leading to hospitalization within this group, however these studies varied in their study populations, severity of cases, age, and comorbidities [Kellner et al., 1989; Juven et al., 2000; Kusel et al., 2006; Miller et al., 2007; Bonzel et al., 2008; Franz et al., 2010; Iwane et al., 2011]. Clinical signs and symptoms of HMPV infection overlap with those of RSV and *rhinovirus* infections and reliable clinical distinction is not possible. Some reports have tried to correlate laboratory parameters such as specimen viral load with disease severity [Bosis et al., 2008; Martin et al., 2008; Houben et al., 2010].

The *Human Metapneumovirus* (HMPV) is related to RSV. Both are members of the *Paramyxoviridae* family and share several epidemiologic and clinical characteristics, HMPV, however affect children of a slightly older age than RSV [Cuevas et al., 2003; Martin et al., 2008; Gaunt et al., 2009]. A previous study found [Franz et al., 2010] that the median age of children with rhinovirus infections was 1.4 years in contrast to children with RSV infections (median

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0.5 years). This finding has been confirmed by others [Korppi et al., 2004]. Since the clinical manifestation and the disease severity depend substantially on the age, a direct comparison of the clinical course of HMPV, RSV, and RV infection is made more difficult by the different average age at presentation.

In the present study three groups of children with comparable age distribution hospitalized with RSV, HMPV or RV infections were compared to minimize this age bias.

PATIENTS AND METHODS

During a 2-year period from November 2006 to October 2008 nasopharyngeal aspirates of children aged 0–16 years hospitalized for a respiratory tract infection at the University Children's Hospital Düsseldorf were investigated. Nasopharyngeal aspirates (NPA) were collected on the day of admission. Out of this collective three groups each encompassing 30 individuals with either HMPV, RSV or RV infection were defined. There were only minor differences in the age distribution as measured by both, the mean age and the range. This was done because in children in the second year of life HMPV, RSV, and RV are frequently found in contrast to very young children who are mostly infected and hospitalized by RSV. These older children are thought to be beyond the period of maternal immunity. Each patient was included only once and no patient was included if more than one viral pathogen was detected.

All specimens were submitted to the Institute of Virology of the University Hospital Düsseldorf and evaluated for RSV (subtype A and B), RV (species A, B, and C), *influenza types A and B, parainfluenza types 1, 2, and 3, enterovirus, adenovirus, human metapneumovirus, coronaviruses 229E, OC43, and NL63* and *human bocavirus* using a quantitative real-time RT-PCR as described elsewhere [Bonzel et al., 2008]. Quantitation for HMPV-, RSV-, and Rhinovirus-genomes was performed using known concentrations of plasmids containing the target regions of the viruses. A standard graph of the C_T values obtained from serial dilutions of the standard was constructed by the software, the C_T values of the unknown samples were plotted on the standard curves and the number of genomes was calculated. Quantitation of Interleukin-8 (IL-8) was performed using a purified anti-cytokine capture antibody (Cat. No. 554716, BD Biosciences, Heidelberg, Germany), a biotinylated anti-cytokine detection antibody (Cat. No. 554718, BD Biosciences, Heidelberg, Germany), and recombinant human IL-8 (Cat. No. 554609, BD Biosciences, Heidelberg, Germany) as a standard in concentrations from 4.0 pg/ml to 500 pg/ml. Standard curves were calculated using the Magellan™ software (Tecan, Crailsheim, Germany). The capture antibody was bound to 96-well microtiter plates at a concentration of 2 μg/ml binding solution. Cell-free supernatants of nasopharyngeal aspirates were diluted 1:10 and 1:20 in blocking buffer (PBS-Tween) and tested in duplicate. Samples with IL-8 concentration above the highest standard were retested at higher dilutions.

Clinical data collected from patient's medical files included gender, prematurity, the presence of chronic underlying diseases, clinical diagnosis, duration of hospitalization, need for oxygen treatment, antibiotic use, chest radiography findings, presence of fever, white cell count, C-reactive protein, and IL-8 concentration in NPA. Leucocytosis was defined as values above 15,000/μl and a significantly raised C-reactive protein (CRP) when raised above 5 mg/dl (normal value <5 mg/dl). Pneumonia was defined using WHO criteria in those patients who underwent chest radiography. Severe respiratory tract infections (sRTI) was defined as the presence of pneumonia, acute viral wheeze (obstructive bronchitis), and bronchiolitis. Bronchitis, upper respiratory tract infection, and two cases of other respiratory tract infections (one patient with underlying chronic lung disease and one with otitis media) were grouped as mild respiratory tract infections (mRTI). Values are expressed as percentages for discrete variables, or as mean and standard deviation for continuous variables, except age and days of hospitalization, which are described by their median.

The data were analyzed using SigmaStat 3.5 and GraphPad Prism 5.01. Categorical data were studied using Fisher's exact test or Pearson's chi-square test, depending on the sample size. Quantitative data were analyzed by the non-parametric Mann-Whitney U test for two groups and by the one way ANOVA test for more than two groups. The 95% confidence interval (95% CI) for proportions was calculated using the modified Wald method. A two sided P-value <0.05 was considered statistically significant. Sample collection and diagnostic procedures were conducted for the purpose of the guidelines of good clinical practice. The study was approved by the Institutional Review Board of the University Hospital Düsseldorf.

Results

Demographic characteristics and medical history are shown in Table I. As described above the three groups of patients were of similar age with a median value of 551 (45–2386) days for HMPV, 525 (110–2250) days for RSV, and 522 (44–2779) days for Rhinovirus. All other characteristics were not significant different.

The clinical diagnoses, presentations and findings are shown in Table II. Pneumonia, acute viral wheeze, and bronchiolitis (severe respiratory tract infections, sRTI) was highest in RSV-patients (23/30, 77%) but did not differ significantly between the three groups. Viral load in nasopharyngeal aspirates showed no statistically significant correlation to the

TABLE I. Comparison of Demographic Characteristics and Medical History in Children With HMPV, RSV and *Rhinovirus* Infection

Characteristic	HMPV (n = 29)	RSV (n = 30)	Rhinovirus (n = 30)	*p*
Median age (days)	551	524,6	521,8	0.664
Gender (male)	19 (66)[a]	16 (53)	15 (50)	0.451
History of prematurity	3 (10)	4 (13)	6 (20)	0.559
History of heart diseases	3 (10)	4 (13)	3 (10)	0.904
History of pulmonary diseases	0	1 (3)	1(3)	0.610
History of neurological diseases	1 (3)	1 (3)	0	0.594
History of chromosome disorder	1 (3)	1 (3)	0	0.594
History of innate metabolic diseases	1 (3)	0	2 (7)	0.359

[a]number, in parentheses percent.

disease severity in any group. The median HMPV viral load was $1.6 \times 10E6$ in the mRTI group (range $1.2 \times 10E6$–$2.5 \times 10E8$) and $9.9 \times 10E7$ in the sRTI group (range $5.0 \times 10E6$–$1.7 \times 10E7$) ($P = 0.08$). The median RSV viral load was $7.2 \times 10E7$ in the mRTI group (range $2.6 \times 10E4$–$1.7 \times 10E8$) and $2.0 \times 10E7$ in the sRTI group (range $2.3 \times 10E2$–$5.4 \times 10E8$) ($P = 0.84$), and the median RV viral load was $1.1 \times 10E6$ in the mRTI group (range $5.1 \times 10E3$–$3.1 \times 10E8$) and $8.8 \times 10E5$ in the sRTI group (range $5.6 \times 10E3$–$2.8 \times 10E9$) ($P = 0.45$). Initiated treatment such as oxygen requirement, frequency of chest X-rays, initiation of antibiotic treatment showed no significant difference between the three groups, although a non significantly higher oxygen requirement was found in RSV-infected children (Table II). Patients with *rhinovirus* infections had a tendency for shorter stay in hospital with a median of 3 days, but the difference was not statistically significant ($P = 0.38$). Children with HMPV infections were dismissed from hospital after a median of 5.5 days and those with RSV infections after 4 days (Fig. 1, top). *Rhinovirus* patients had a significantly lower body temperature compared to HMPV- and RSV-patients (37.8°C vs. 38.7°C for HMPV and 38.7 for RSV, $P = 0.006$) (Fig. 1, middle). The leucocyte count (Fig. 1) showed a significantly higher value in *rhinovirus* patients ($14.1 \times 10E3/\mu l$, 11.8–16.3) as compared to HMPV-patients ($10.7 \times 10E3/\mu l$, 9.0–12.4) and RSV-patients ($12.2 \times 10E3/\mu l$, 10.8–13.7) ($P = 0.035$). No notable differences in the C-reactive protein values between the three groups was observed.

The most significant difference could be found in the determination of IL-8 concentration in NSA: in *rhinovirus* patients the IL-8 concentration was 2.35 μg/ml (0.2–194) in contrast to HMPV-patients (median 9.2, 1.0–139), and RSV-patients (median 10.8, 0.1–59.5) ($P < 0.05$) (Table II).

DISCUSSION

HMPV and RSV generally circulate in the community during the winter seasons along with the *influenza viruses* and some other respiratory viruses [van den Hoogen et al., 2003; van den Hoogen et al., 2004; Mejias et al., 2004; Williams et al., 2004; Williams, 2005; Williams et al., 2005]. In contrast *rhinovirus* infections is found during the whole year with peaks in spring and autumn [Monto, 2002a, 2002b].

In young children the clinical picture of most respiratory infections tends to be more severe, but a straightforward correlation between clinical presentation and

TABLE II. Comparison of Clinical Diagnosis, Presentation and Findings in Children With HMPV, RSV, and *Rhinovirus* Infection

Characteristic	HMPV	RSV	Rhinovirus	*p*
Severe RTI	13/27(48)	23/30(77)	16/25(64)	0.083
Pneumonia	8/27 (30)	14/30 (47)	8/25 (32)	0.435
Obstructive bronchitis	5/27 (19)	8/30 (27)	9/25 (36)	0.364
Bronchiolitis	1/27 (4)	2/30 (7)	0/25 (0)	0.423
Milder RTI				
Bronchitis	9/27 (33)	5/30 (17)	5/25 (20)	0.298
URTI	2/27 (7)	1/30 (3)	3/25 (12)	0.470
Other	2[a]/27 (7)	0/30 (0)	0/25 (0)	0.123
Temperature (°C) (Mean, 95%CFI)	38.7 (38.2–39.2)	38.7 (38.3–39.1)	37.8 (37.3–38.2)	0.006
Leukocytes tsd/μl (Mean, 95%CFI)	10.7 (9.0–12.4)	12.2 (10.8–13.7)	14.1 (11.8–16.3)	0.035
CRP ≥ 0,5 mg/dl	13/22 (59%)	19/29 (66%)	17/23 (74%)	0.574
IL-8 μg/ml (Mean, 95 CFI)	25.1 (11.53–38.7)	12.02 (7.57–16.47)	6.33 (0.02–12.65)	<0.05 [b]
Oxygen requirement	6/22 (27%)	13/29 (44%)	6/23 (26%)	0.271
Lenght of stay (median)	5,5	4	3	0.387
Antibiotic treatment	11/22 (50%)	14/28 (50%)	13/23 (56%)	0.873

[a]1 × underlying chronic lung disease and 1 × otitis media.
[b]HMPV/RSV versus Rhino.

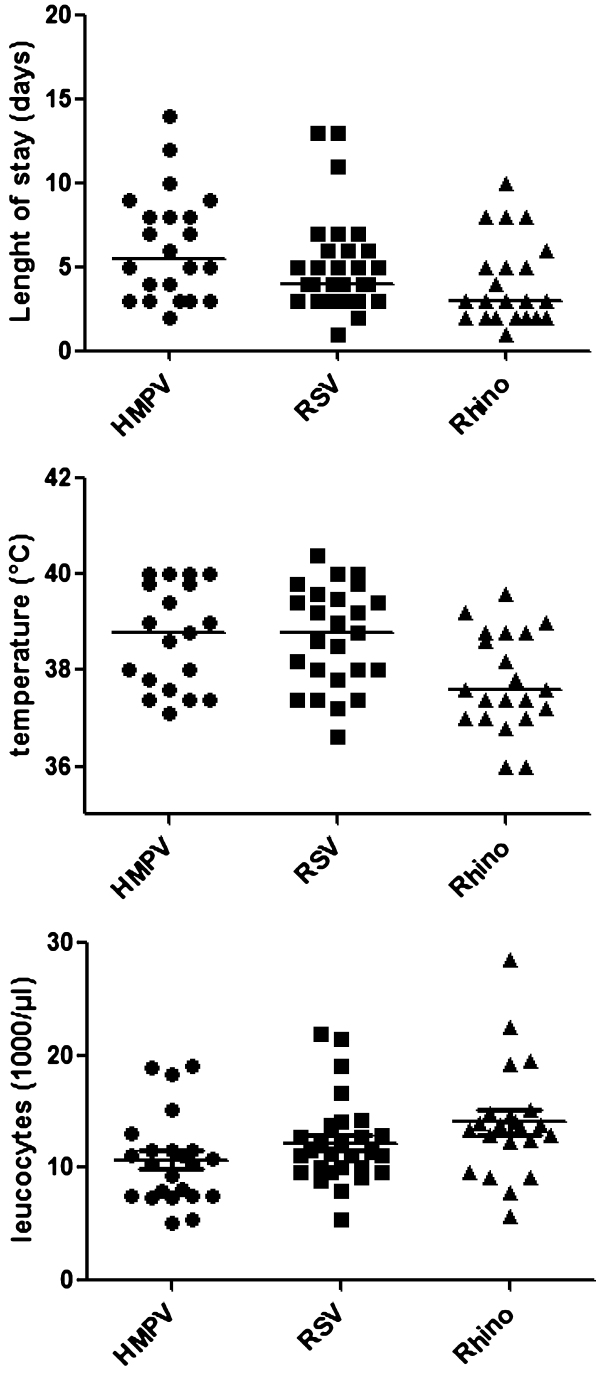

Fig. 1. Length of stay, temperature, and leucocyte count on the day of admission of children infected with HMPV, RSV, or Rhinovirus. The horizontal lines represent median values.

the causing respiratory pathogen is absent. Therefore, in the present study hospitalized children with RSV, HMPV, or RV infections and comparable age distribution were compared to minimize the effects of age on the clinical manifestation. It was found that *rhinovirus* infections could not be differentiated clearly by clinical signs and laboratory parameters on admission from HMPV and RSV infections. The frequency of severe respiratory tract infection was similar between the three groups however some differences could be found regarding the course of illness. Several recent studies compared the clinical signs and the severity mainly between HMPV and RSV with conflicting results. Most studies have found no clear difference [Mullins et al., 2004; Wolf et al., 2006], however some reports describe more severe infections in patients with HMPV or RSV [von Linstow et al., 2004; Wilkesmann et al., 2006]. This could be due to different study populations and an age-related frequency of severe manifestations. The third group of the present study, the *rhinovirus*-infected children showed clinical courses with significantly lower body temperature and a non-significant shorter length of stay in hospital. This slightly milder course could be predicted neither by regarding the standard laboratory parameters at admission nor by the more sophisticated determination of the viral loads in the nasopharyngeal aspirates. The finding of higher leucocyte counts in RV-infected patients as compared to HMPV- and RSV-infections is in agreement with previous studies [Franz et al., 2010] and might be due to an immune suppressive effect of the latter.

Determination of the viral load in respiratory tract infections has been investigated in the past by several groups [Bosis et al., 2008; Martin et al., 2008; Franz et al., 2010; Houben et al., 2010]. In a recent study, a difference in the viral load of most viruses between the date of admission and a second sample several days later and between mono- and mixed infections could be found. In this study, a correlation between viral load and the severity of lower respiratory tract infection was not found in contrast to other reports [Bosis et al., 2008; Martin et al., 2008; Houben et al., 2010].

The most significant difference in laboratory parameters was seen with nasopharyngeal IL-8 concentrations, which was significantly lower in patients with *rhinovirus* infections. IL-8 also known as neutrophil chemotactic factor, is a member of the CXC chemokine family and induces chemotaxis in neutrophils and other granulocytes, causing them to migrate towards the site of infection and initiate phagocytosis [Baggiolini and Clark-Lewis, 1992; Baggiolini et al., 1994; Baggiolini et al., 1995]. IL- 8 is often associated with localized inflammation and has been described as a proinflammatory mediator [Vlahopoulos et al., 1999]. There are conflicting results in the literature concerning the correlation of cytokine concentrations in the respiratory specimens and the underlying virus. The role of acute phase cytokines (IL1β, IL-6, TNFα) in the nasopharynx during upper respiratory infections with *influenza virus, adenovirus, enterovirus*, and *rhinovirus* in children were also investigated by others [Patel et al., 2009]. They found significantly higher IL-6 concentration during *adeno* virus and *influenza* virus infections as compared to rhinoviruses and generally in children with systemic febrile response during upper respiratory infection.

In contrast, others compared RSV lower respiratory tract infections with rhinovirus lower respiratory tract infection and determined a variety of cytokines and chemokines and could only find a significant difference for IL-15 but not for IL-6 or IL-8 [Garcia et al., 2012]. However, the latter study enrolled less than 20 children in each study group younger than 2 years. The former studies are in agreement with the data presented here showing lower concentrations of the proinflammatory cytokine IL-8 in children with *rhinovirus* infections as compared to HMPV- and RSV-infections and a tendency to lower body temperature. The lower concentrations of the chemotactic factor IL-8 in the nasopharyngeal aspirates contrasts to the higher leucocyte counts in the blood of the *rhinovirus* infected children underlining that local and systemic immune responses might show different patterns. Increased or prolonged inflammatory responses have been discussed as a reason for a higher disease burden [Turner et al., 1998; Gern et al., 2000; Gern et al., 2002]. Nevertheless, it remains to be elucidated if a shorter hospital stay in children with *rhinovirus* infections indeed correlates with lower concentrations of IL-8 in the nasopharynx.

There were several limitations to the present study. For some patients the documentation of clinical parameters was not complete and a higher number of patients would be necessary to reach higher levels of significance of parameters as length of stay and leucocyte counts. This is supported by a former prospective study [Franz et al., 2010] where significant differences between these two parameters could be found. Finally, a control group of healthy children was not enrolled, unfortunately a common fault in many studies of pediatric patients. Taken together the present data lead to the conclusion that a reliable identification of a HMPV, RSV, or RV infection can only be made by a molecular techniques such as qualitative real time PCR. In contrast quantitation of virus was, in this context, not useful for the assessment of the severity or duration of the disease. Where HMPV- and RSV-infections were quite similar in their clinical course, *rhinovirus* infections seem to have a tendency to faster recuperation in young children.

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