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LETTER TO THE EDITOR

Comparison of bronchiolitis of human metapneumovirus and human respiratory syncytial virus

Y. WANG[1], W. JI[1*], CH. HAO[1], Y. D. YAN[1], X. SHAO[2], J. XU[2]

[1]The Department of Respiratory Medicine, Children's Hospital Affiliated to Soochow University, Suzhou 215003, P. R. China; [2] The Department of Clinical Laboratory, Children's Hospital Affiliated to Soochow University, Suzhou 215003, P. R. China

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Bronchiolitis is an important cause of illness and death in infants. Approximately 3% of children under the age of 1 year are hospitalized annually for bronchiolitis, and the cost of hospitalization is estimated to exceed $700 million (*1,2*). Human respiratory syncytial virus (HRSV) is the most common virus associated with bronchiolitis (*3–5*). Human metapneumovirus (HMPV) was first identified in The Netherlands in 2001 and subsequent studies have indicated that HMPV is a critical viral pathogen implicated in acute respiratory tract infections in children. The clinical symptoms associated with HMPV infection range from upper airway disease to severe bronchiolitis and pneumonia (*6–11*). There are, however, no studies on HMPV bronchiolitis in children from Southeast China. We hypothesize that HMPV may be an important pathogen causing acute bronchiolitis in infancy. The objective of our study was to determine the incidence and clinical features of HMPV bronchiolitis and to compare these characteristics with those associated with HRSV infection.

*Corresponding author. E-mail: wrxwrb@126.com; phone: +86 51267788302.

Abbreviations: FLUAV = influenza A virus, FLUBV = influenza B virus; HBoV = human bocavirus; HMPV = human metapneumovirus; HRSV = human respiratory syncytial virus; PIV I = parainfluenza virus I; PIV II = parainfluenza virus II; PIV III = parainfluenza virus III

The present study was carried out in the Department of Respiratory Medicine and Intensive Care Unit, Children's Hospital Affiliated to Soochow University on children admitted with the diagnosis of bronchiolitis from January 2010 to December 2013. The bronchiolitis was diagnosed based on the guidelines described by Zhu Futang Practical Pediatrics, 7th Edition (*12*). Patients who presented with the following findings were excluded from the study: prematurity, heart diseases, chronic pulmonary diseases, congenital airway malformations and immunodeficiencies.

Nasal aspirate samples were obtained from each patient within 24 hr of admission by introducing a sterile plastic catheter into the lower part of the pharynx via the nasal cavity. The nasal aspirates were subjected to direct immunofluorescence assay (Chemicon Internation Inc. Temecula, CA USA) to detect adenovirus, HRSV, influenza A and B virus (FLUAV and FLUBV), and parainfluenza virus (PIV) I, II, and III. We designed a primer pair to specifically amplify a fragment of 213 bp (562–774) of the N gene of HMPV sequence available from the GenBank database (Acc. No. AF371367). Primers were synthesized by Shanghai Sangon using the sequences as follows: sense, 5'-AACCGTGTACTAAGTGATGCACTC-3'; antisense, 5'-CATTGTTTGACCGGCCCCATA A-3'. The presence of HMPV genome was confirmed by RT-PCR of HMPV RNA. Viral RNA was extracted with Trizol reagent (Invitrogen). PCR assays were performed in an automatic PCR cycler

(Perkin Elmer, USA) under the following conditions: 45 cycles of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec and extension at 68°C for 30 sec. The final extension was carried out at 68°C for 7 min. The PCR products were separated by 1.5% agarose gel electrophoresis and visualized by ethidium bromide staining. Positive results were indicated by the appearance of a 213-bp band under ultraviolet detection. Ten positive PCR products were randomly selected, recovered from agarose gel and sequenced. Human Bocavirus (HBoV) DNA (a tentative member of the genus *Bocavirus*) was detected by real-time PCR. The cyclic temperature settings were 94°C, 30 sec; 56°C, 30 sec; 72°C, 30 sec; repeated in 40 cycles. The primer sequences were: sense, 5'-TGACATTCAACTACCAACAACCTG-3'; antisense, 5'-CAGATCCTTTTCCTCCTCCAATAC-3' and HBoV probe: 5'-FAM-AGCACCACAAAACACCTCAG GGG-3'-TAMRA.

A total of 942 children with bronchiolitis were studied, including 225 cases in 2010, 205 in 2011, 244 in 2012 and 268 in 2013. There were 644 (68.4%) male and 298 (31.6%) female patients. 362 (38.4%) were younger than 6 months of age, 317 (33.7%) were between 6 months and 1 year of age and 263 (27.7%) were between 1 and 2 years of age.

We identified at least one virus in 68.3% of samples from 942 children with bronchiolitis. HRSV was the most common virus detected (50.3%), followed by PIV III (6.1%) and HBoV (5.3%). HMPV was detected in 4.8% of cases, indicating that HMPV was an important pathogen in bronchiolitis. The annual HMPV-positive rates were 5.3% (2010), 7.3% (2011), 2.9% (2012), and 4.1% (2013). HMPV was detected with epidemic peaks in 2010 and 2013 between January and May, and in 2011 and 2012 between January and April, indicating its prevalence in the spring each successive year. On the other hand, the highest rates of HRSV infection were observed between October of one year and March of the following year, indicating its prevalence in winter. The seasonality of these two viral infections was clearly different.

The main clinical manifestations of brochiolitis with HMPV infection included cough (100%), wheezing (100%), fever (33.3%), tachypnea (13.3%), dyspnea (6.7%), cyanosis (6.7%), and lung rales (93.3%). Abnormalities also appeared on chest radiograph (73.3%), including patchy shadows, increased and blurred bilateral lung markings and emphysema. These clinical symptoms of HMPV infection did not differ much from HRSV. The similarity of clinical symptoms between HMPV infections and HRSV infections identified in our study is consistent with earlier studies (*13–16*). Nevertheless, we found that the mean age of HMPV-infected children of 8.50 ± 6.23 months was higher than the mean age of 6.15 ± 4.54 months of the HRSV-infected children (P <0.001). Tachypnea, dyspnea, cyanosis, SaO_2 <90% and Paediatrics intensive care unit (PICU) admission were significantly less common in children with HMPV than in those with HRSV infections (P <0.001). Patchy shadows on chest X-ray were more common in children infected with HMPV than in those with HRSV (60.6% vs. 11.2%, P <0.001), while chest hyperinflation was more commonly observed in children with HRSV infection (62.7% vs. 15.2%, P <0.001). The average hospital stay with HMPV infection was 7.36 ± 2.72 days, which is shorter than that of HRSV-infected patients at 9.89 ± 2.73 days (P <0.01), suggesting that HMPV probably causes a milder illness than HRSV. Wolf *et al.* previously reported that patients with HMPV bronchiolitis needed less oxygen, and had a shorter duration of hospital stay and lower rates of PICU admissions (*17*).

Table. Frequency of respiratory viruses in nasal aspirate samples with bronchiolitis (a single virus was detected in 643 (68.3%) children and multiple viruses were detected in 22 (2.3%) children with bronchiolitis)

Pathogens	n* (%)
HRSV	474 (50.3)
PIV III	57 (6.1)
HBoV	50 (5.3)
HMPV	45 (4.8)
FLUBV	9 (1)
FLUAV	7 (0.7)
PIV 11	1 (0.1)
Two viruses	
HMPV-HBOV	4 (0.4)
HBOV-PIV III	4 (0.4)
HRSV-FLUAV	4 (0.4)
HRSV-HBoV	3 (0.3)
HMPV-HRSV	3 (0.3)
HMPV-PIV III	2 (0.2)
HRSV-PIV III	2 (0.2)

*n = 942.

To summarize, our study reveals that HMPV is an important cause of bronchiolitis with an epidemic peak in spring. Clinical characteristics of HMPV infections are similar to HRSV, but HMPV bronchiolitis seems to be a milder disease than that caused by HRSV.

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