Human parechovirus infection in Hong Kong neonates, infants, and young children: abridged secondary publication

PKS Chan *, MCW Chan, EAS Nelson, TF Leung

KEY MESSAGES

1. Human parechovirus (HPeV) infection occurred in about 2.3% of all young children (≤3 months) hospitalised for acute viral illnesses.
2. HPeV infection exhibited a distinct seasonality, with most infections occurring in September to January (autumn and winter).
3. The more pathogenic type, HPeV3, was rare in Hong Kong.
4. Clinical presentation of HPeV ranged from mild gastroenteritis, upper respiratory tract infection, and febrile rash to convulsion and severe sepsis.
5. Diagnostic service for HPeV should be made available for young infants presenting with sepsis.

Hong Kong Med J 2020;26(Suppl 4):S8-11
HMRF project number: 13120362

[1] PKS Chan, [1] MCW Chan, [2] EAS Nelson, [2] TF Leung

[1] *Department of Microbiology, The Chinese University of Hong Kong, Hong Kong*
[2] *Department of Paediatrics, Prince of Wales Hospital, Hong Kong*

* Principal applicant and corresponding author: paulkschan@cuhk.edu.hk

Introduction

There are 16 types of human parechovirus (HPeV), which is fastidious to grow and can escape detection by polymerase chain reaction (PCR) based on pan-enterovirus primers. Most laboratories do not offer testing for HPeV, and therefore many epidemiological and clinical aspects of this virus remain unknown.

Currently available data indicate that HPeV1 is the most common type found and is associated with mild gastrointestinal illnesses. HPeV3 is more often associated with severe diseases (including sepsis and meningoencephalitis), especially in neonates.[1]

Methods

This 24-month prospective study was conducted at the Prince of Wales Hospital in Hong Kong that has a catchment population of about 650 000 including about 25 000 children under 5 years old. During the study period, children aged ≤36 months who were admitted to the hospital for suspected acute viral illnesses were identified. A targeted number of patients from each age group were randomly selected for study every week. Specimens were tested for HPeV, in addition to the routine virological and bacteriological investigations. This study was approved by the Joint Chinese University of Hong Kong – New Territories East Clinical Research Ethics Committee.

HPeV RNA was detected by real-time PCR,[2] and genotype was assigned based on the maximum likelihood tree topology constructed using RAxML MPI v8.2.8 based on the global nucleotide alignment of the VP1 gene sequences. The distribution in HPeV types observed in this study was compared to that reported worldwide by the weighted GUniFrac method.

Children with symptoms of acute gastroenteritis were tested for rotavirus and norovirus on a routine basis. Stool samples positive for HPeV were subjected to multiplex PCR, which is capable of detecting viruses associated with acute gastroenteritis, including rotavirus, norovirus, adenovirus 40/41, sapovirus, astrovirus, and aichi virus.

Results

A total of 3911 children were recruited between March 2014 and February 2016, with 129 to 225 examined per month. The male-to-female ratio was 1.3:1, and 7.3% were neonate, 37.0% were 4 weeks to 12 months, 30.4% were 13 to 24 months, and 25.4% were 25 to 36 months.

A total of 4567 specimens collected from the 3911 children were tested for HPeV: 58.0% were nasopharyngeal aspirate (NPA) samples; 32.5% were stool samples or rectal swabs; 4.4% were cerebrospinal fluid; and 5.0% were blood and other miscellaneous samples.

Of the 3911 children, 49 boys and 39 girls were detected to have HPeV. Of them, 3 (3.4%) were neonates, 40 (45.5%) were aged 4 weeks to 12 months, 29 (33.0%) were aged 13 to 24 months, and 16 (18.2%) were aged 25 to 36 months.

A sharp seasonality was observed with 87.5% (77/88) of infections detected between September and January, corresponding to the autumn and

winter seasons in Hong Kong (Fig 1). The same seasonal pattern was observed in both years.

Of the 88 children infected with HPeV, 80 (90.9%) had samples with virus type identified. In both seasons, HPeV1 predominated and accounted for 81.3% (65/80) of infections, followed by HPeV4 (12.5%, 10/80). Other HPeV types were rare: HPeV3 (n=2), HPeV6 (n=2), and HPeV5 (n=1).

The distribution pattern of virus type of the 88 children was compared with that of 20 studies, including one from Hong Kong. The distribution pattern of HPeV types could be broadly divided into three groups based on clustering analysis using the weighted GUniFrac method. The pattern of Hong Kong was close to that reported from Guangzhou (China), Lanzhou (China), and Thailand where HPeV1 predominated with a small number of HPeV3/4. In contrast, HPeV3 predominated in studies from Japan, Denmark, Spain, France, and United Kingdom. The Netherlands, Italy, Taiwan, Japan, and China have reported a co-circulation of both HPeV1 and HPeV3 types.

Children with HPeV1 infection were significantly older than those with non-HPeV1 infection (12 [9-19] months vs 7 [6-17.5] months, P=0.450).

Regarding clinical presentation, when HPeV was the only infection identified, it was regarded as having a 'probable' association with the illness. When HPeV was detected in association with other conventional pathogens of the illness, the role of HPeV was regarded as 'uncertain'. Because the association between respiratory and gastrointestinal pathogens with neurological presentation is less clear, the role of HPeV was regarded as 'suspected' in these cases (Fig 2).

For acute gastroenteritis, 27 (30.7%) of the 88 infected children were regarded as having HPeV being a 'probable' cause. Among them, 25 (92.6%) had diarrhoeal symptoms, with the frequency varying from once a day to >10 times a day. In contrast, only 12 (44.4%) of 27 children had vomiting, which was usually mild. Four children also had HPeV detected from NPA, with two of them being coinfected with parainfluenza type 2 or respiratory syncytial virus and all having respiratory symptoms. In addition, 30 (37.5%) of the 88 infected children had symptoms of acute gastroenteritis and HPeV detected from stool, but the role of HPeV was regarded as 'uncertain', because other gastroenteritis-associated pathogens (most commonly norovirus, rotavirus, *Salmonella* and *Campylobacter spp*) were also found in stool samples. Four of the 30 children also developed rash.

For acute respiratory illness, 11 (12.5%) of the 88 HPeV-infected children were regarded as having HPeV being a 'probable' cause. The most common symptoms were cough and runny nose. Five children had mild shortness of breath or noisy breathing, and one developed pneumonia with chest X-ray showing mild left perihilar haziness but without significant consolidation. Six (54.5%) of the 11 children also had HPeV detected from stool. Five children also developed symptoms of acute gastroenteritis, with two having coinfection with *Salmonella enteritidis* or *Campylobacter jejuni*. In addition, 20 children with HPeV detected from NPA also had coinfection with other respiratory pathogens; 12 (60.0%) of them developed lower respiratory tract involvement with acute bronchiolitis or pneumonia.

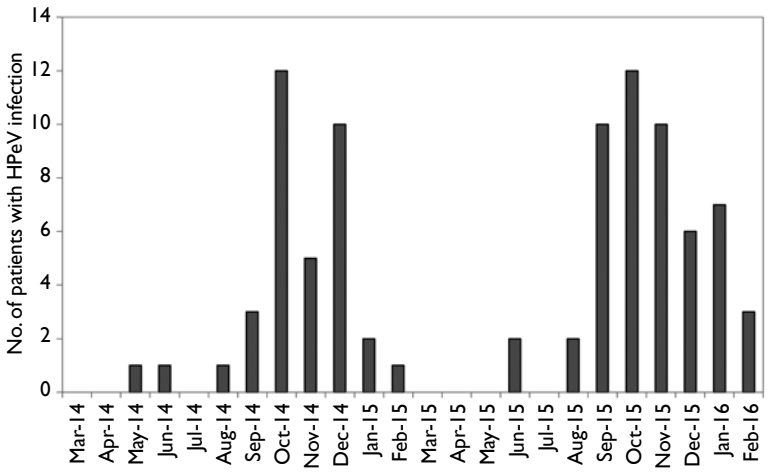

FIG 1. Temporal distribution of human parechovirus (HPeV) infections in Hong Kong.

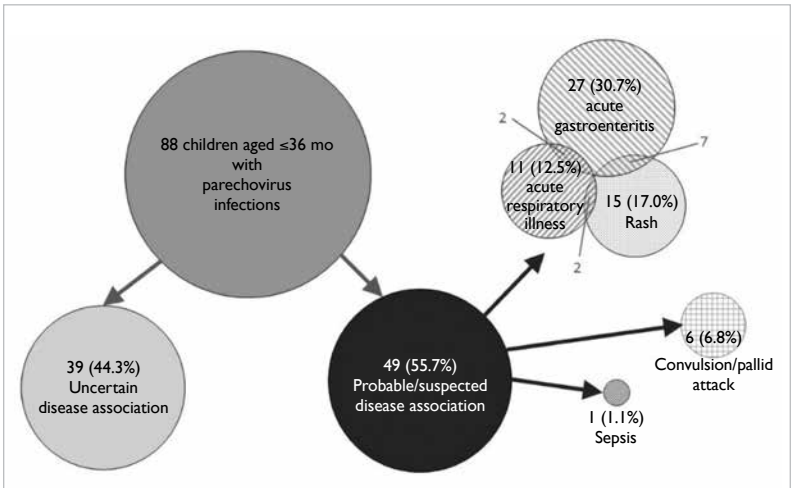

FIG 2. **Overview on major illnesses of 88 children with human parechovirus (HPeV) infection:** cases without coinfecting pathogen that could have accounted for the illness were considered as having a 'probable' disease association with HPeV. Six children with convulsion or pallid attack who were coinfected with pathogen not typically associated with neurological manifestation were considered as having a 'suspected' disease association with HPeV. 'Uncertain' disease association referred to children coinfected with pathogen(s) that typically associate with the presenting illness.

TABLE 1. Characteristics of human parechovirus (HPeV)–infected children with rash illness

Case No.	Sex/ age, m	Presentation of rash	Concurrent illness(es)	Sample(s) positive for HPeV	HPeV type	Coinfections
16	M/30	Itchy blanchable maculopapular rash over back, spread to trunk, forearms, and feet.	Acute gastroenteritis	Stool	HPeV1	Rhinovirus and non-typhoidal *Salmonella spp*
24	M/7	Mild fine blanchable maculopapular rash over face, trunk, and right scrotum, sparing limbs. Developed after fever subsided. Clinically considered as roseola.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV4	-
27	F/9	Maculopapular rash over face and body. Developed after fever subsided. Clinically considered as roseola.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV1	-
34	F/19	Maculopapular rash over buttock and hands, with fever for 3 days.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV1	Parainfluenza virus type 1
43	M/6	A few spots of rash over back, face, and neck, with fever for 9 days.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV4	Rhinovirus, non-typhoidal *Salmonella spp*
49	M/10	Generalised whole body maculopapular rash, with fever for 2 days.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV1	-
50	M/16	Maculopapular rash over trunk after fever subsided. Clinically considered as roseola.	Acute gastroenteritis	Stool	Typing failed	-
51	F/3	Eczematous rash over chest, with fever.	Acute gastroenteritis, bronchiolitis	Stool	HPeV1	Respiratory syncytial virus
57	F/20	Blanchable macular rash over forehead, erythematous periorbital swelling, with fever.	Upper respiratory tract illness	Stool, blood	HPeV4	-
58	M/11	Generalised maculopapular rash. Developed after fever subsided. Clinically considered as roseola.	Upper respiratory tract illness	Stool, nasopharyngeal aspirate	HPeV1	-
67	F/20	Itchy rash over trunk and spread to limbs and scalp, weeping, crusting, peeling, and sandpaper-like. Features of cellulitis. No fever.	-	Rectal swab	HPeV4	*Staphylococcus aureus* from skin swab
68	M/8	Eczematous rash, with fever.	Acute gastroenteritis, croup, pneumonia	Stool	HPeV4	-
76	F/7	A few patches of maculopapular rash over right hand only, no fever.	Acute gastroenteritis, upper respiratory tract illness	Stool	HPeV4	Norovirus, rhinovirus
77	F/7	On and off skin rash, faint scattered spots over face and trunk.	Acute gastroenteritis	Stool, nasopharyngeal aspirate	HPeV1	Norovirus
81	M/16	Mild generalised erythematous patches, with fever.	Bronchiolitis	Nasopharyngeal aspirate	HPeV1	-
87	M/10	Maculopapular rash over trunk. Developed after fever subsided. Clinically considered as roseola.	Upper respiratory tract illness	Stool, nasopharyngeal aspirate	HPeV1	Parainfluenza type 1

For rash, 15 (17.1%) of 88 children were regarded as having HPeV being a 'probable' cause. In all except one child, HPeV was found from stool/rectal swab (Table). The rash presentation was mainly maculopapular and often generalised involving trunk and limbs, and accompanied with fever or developed just after fever had subsided. Most of these children presented with other concurrent illnesses such as acute gastroenteritis and mild upper respiratory tract illness. A 20-month-old girl developed an itchy, weeping, crusting, sand paper-like rash on the scalp and limbs, without fever. The skin swab was positive for *Staphylococcus aureus*. The HPeV4 found in the stool of this child was likely to be a bystander.

Six (6.8%) of the 88 HPeV-infected children developed neurological illnesses, including convulsion (n=5) and pallid attack (n=1). All these children had concurrent illnesses that could be explained by the coinfection identified. Three children had acute gastroenteritis secondary to norovirus or non-typhoidal *Salmonella spp*. Another three children had upper respiratory tract infections with rhinovirus or parainfluenza type 3 virus. Because association between HPeV and coinfecting

pathogens and the neurological presentation could not be verified in these children, HPeV was regarded as a 'suspected' pathogen.

Only one child presented with sepsis. A 6-day-old female neonate born full term by vaginal delivery presented with fever up to 38.6°C, with no respiratory or gastrointestinal symptoms. Her heart rate was 200 beats per min. She was given an intravenous bolus of normal saline of 40 mL/kg body weight but tachycardia and metabolic acidosis persisted despite blood pressure being maintained in the normal range. She was empirically treated with intravenous ampicillin and amikacin. Her infection markers including white cell count and C-reactive protein were not raised, despite presentation of impending shock. Ultrasonographic examination of abdomen was unremarkable. Blood, urine, and cerebrospinal fluid cultures were all negative. Chest X-ray showed only mild bilateral lung field streakiness. Her NPA was positive for HPeV3, which was the only pathogen identified.

The six children presenting with neurological illness in which HPeV was regarded as a 'suspected' cause were significantly older than other children who presented with acute gastroenteritis (25 [22.5-29.0] months vs 11.0 [7-15.5] months, P<0.01), acute respiratory illness (25 [22.5-29.0] months vs 13.0 [10.5-18.5] months, P<0.01), and rash (25 [22.5-29.0] months vs 10.0 [7-16] months, P<0.01).

Discussion

The distribution pattern of virus type of the 88 children was very similar to that reported from Guangzhou where travel of people is very frequent.[3] In contrast, HPeV3 was rarely detected in Hong Kong (2/80, 2.5%), although it is commonly found in Europe and a few Asian cities. This may have implications on local disease burden, as HPeV1 is more likely to be associated with mild gastroenteritis, and HPeV3 is more likely to be associated with severe diseases (including sepsis, meningoencephalitis, and myocarditis) in infants below the age of 3 months.[4]

In Hong Kong, the prevalence of HPeV4 is relatively high, which is also seen in nearby cities. HPeV4 occurred more frequently in children with rash illness. A characteristic pattern of rash with palmar-plantar distribution has been described in young infants infected with HPeV3.[5] However, the presentation of rash illness associated with other HPeV types, or in older infants and young children is less well defined. In the current study, most children who developed a generalised maculopapular rash mainly involved face and limbs and accompanied with fever.

We suspect coinfection of HPeV with other respiratory viruses may confer a higher chance of low respiratory tract involvement, as 60% of these children had acute bronchiolitis or pneumonia.

Conclusions

HPeV infection had a clear seasonality in Hong Kong and was found in 2.3% of all children aged ≤36 months hospitalised for suspected acute viral illnesses. In about half of the cases, HPeV probably contributed to the disease, most commonly acute mild acute gastroenteritis, upper respiratory tract infection, and generalised maculopapular rash. Sepsis was found in a neonate. Further study is warranted to clarify the role of HPeV in causing convulsion and aggravating other respiratory viral infections. Diagnostic service for HPeV should be made available for young infants presenting with sepsis.

Funding

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR (#13120362). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

(1) Chiang GPK, Chen Z, Chan MCW, et al. Clinical features and seasonality of parechovirus infection in an Asian subtropical city, Hong Kong. PLoS One 2017;12:e0184533.

References

1. de Crom SC, Rossen JW, van Furth AM, Obihara CC. Enterovirus and parechovirus infection in children: a brief overview. Eur J Pediatr 2016;175:1023-9.
2. Nix WA, Maher K, Johansson ES, et al. Detection of all known parechoviruses by real-time PCR. J Clin Microbiol 2008;46:2519-24.
3. Chen H, Yao Y, Liu X, et al. Molecular detection of human parechovirus in children with acute gastroenteritis in Guangzhou, China. Arch Virol 2014;159:971-7.
4. van der Sanden S, de Bruin E, Vennema H, Swanink C, Koopmans M, van der Avoort H. Prevalence of human parechovirus in the Netherlands in 2000 to 2007. J Clin Microbiol 2008;46:2884-9.
5. Shoji K, Komuro H, Kobayashi Y, et al. An infant with human parechovirus type 3 infection with a distinctive rash on the extremities. Pediatr Dermatol 2014;31:258-9.