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CLINICAL & BASIC RESEARCH

The Burden of Human Parechoviruses Among Children in Oman

A retrospective study

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abstract: ***Objectives:*** This study aimed to evaluate the burden, clinical and laboratory features and outcomes of human parechoviruses (HPeVs) infection among children in Oman. ***Methods:*** This retrospective study included children (aged <18 years) with molecularly proven HPeV infection who were managed at Sultan Qaboos University Hospital, Muscat, Oman, between January 2017 and December 2019. Data were obtained from the patients' medical records and analysed to describe their demographics, clinical and laboratory features, management and outcomes. ***Results:*** HPeV was detected in 61 patients, 44 (72%) of whom were males. The median age of these patients was nine months (interquartile range [IQR]: 6–15 months). HPeV was detected throughout the year without any significant peaks. Majority of the patients (n = 51, 84%) had co-infection with other viruses. Forty-eight (79%) children with HPeV infection required hospitalisation, and their median length of hospital stay was five days (IQR: 3–8 days). Ex-prematurity (n = 10, 16%) was the commonest comorbidity among this group. Fever (n = 41, 67%) and cough (n = 41, 67%) were the commonest presenting symptoms among the children. Two-thirds of the HPeV-infected children in this cohort were managed for lower respiratory tract infection; none was managed for meningitis. Gastroenteritis was not common in this cohort; only eight children had diarrhoea. All children made a full recovery. ***Conclusion:*** HPeVs infection does not show a clear seasonality in Oman. Most of the children were aged <2 years and had a viral co-infection. The outcomes of HPeV infection were favourable, with no mortalities, but a thorough follow-up for neurological outcomes was lacking.

Keywords: Children; Parechovirus; Infection; Patient Outcome Assessment; Oman.

Advances in Knowledge

- *The majority of the children infected with human parechoviruses (HPeVs) in the current study were male, younger than two years and had a viral co-infection.*
- *HPeV infection does not show a clear seasonality in Oman.*
- *No mortality was reported in this group.*

Applications to Patient Care

- *This study focused on assessing the burden of HPeV infection among children in Oman and describing their clinical and laboratory features.*
- *This study's findings will help paediatricians understand the complete clinical picture and outcomes of infection with this virus in Oman.*

Human parechoviruses (HPeVs) cause gastrointestinal, severe respiratory tract and central nervous system infections in children.[1,2] They belong to the Picornaviridae family, which consists of non-enveloped, positive-sense, single-stranded RNA viruses[3] that are mainly transmitted through respiratory droplets and the faecal-oral route.[4,5] There are two species of HPeVs: Parechovirus A and Parechovirus B.[6] Parechovirus A is further divided into 19 genotypes, with HPeV 1, 3 and 6 being the most common genotypes associated with infection in humans.[6–8] The prevalence and seasonality of the virus differ from place to place based on the different HPeV genotypes and the patient's age.[6]

HPeV infection is usually asymptomatic but can be associated with mild respiratory and gastrointestinal symptoms in children.[8] Some infants present with fever, irritability and rash and are described as 'hot, red and angry babies'.[8] The less common clinical features include seizures, abdominal distension, liver failure and pseudo-appendicitis.[8] It can also be associated with sepsis-like diseases and meningoencephalitis.[7] A study in Iran showed that compared to human enteroviruses, HPeVs were a commoner cause of aseptic meningitis and sepsis-like disease in children less than eight years of age between 2009 and 2011.[9] Another Iranian study reported that among the HPeV genotypes, HPeV-1 was the main cause of diarrhoea.[10]

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Zhu *et al*. reported in their study that HPeV infection was more common in children aged less than two years.[11] Central nervous system involvement in HPeV infections might result in long-term complications including white matter abnormalities, cerebral palsy and neurodevelopmental sequelae.[6,12] Mortality from HPeV infection is rare among otherwise healthy children.[13]

HPeV infection is common worldwide and is not specific to a particular region. Australia reported three HPeV-3 epidemics between 2013 and 2018.[7,8] In several European studies, HPeV infection was seen in about 3–8 % of children presenting to the emergency department with a febrile illness.[8,14,15] The seasonality of the virus is not very clear, but it depends mainly on the most common genotype present in an area.[6] A study in Iran reported a peak in HPeV-1 infection rates during spring and autumn, while Rahimi *et al*. reported that there was no significant season-based variation in the incidence rate of HPeV infections in Iran as it was detected throughout the year.[9,10] HPeV-1 infections occur more in the summer and autumn periods of the year in the USA, Denmark and Australia compared to Germany which showed a decrease in infection rates in the summer.[6,16–18] In Spain, a study showed that the number of HPeV cases increased during both summer and spring.[19] In Hong Kong and Northern Ireland, studies have shown that HPeV infection rates in children are much higher during winter.[2,20,21]

There is limited data on the burden and outcome of HPeV infection among Omani children, and little importance has been given to HPeV infection in the Middle East region. Therefore, the results of this study will help paediatricians and healthcare professionals in Oman and the neighbouring countries to get a better understanding of the burden of this virus in the region. This study aimed to identify all confirmed cases of HPeV infection among children presenting to Sultan Qaboos University Hospital (SQUH), Muscat, Oman, and describe their clinical and laboratory features as well as their outcomes.

Methods

This retrospective study was conducted at SQUH, one of the major tertiary care facilities in Muscat governorate, Oman. The study included all symptomatic children under 18 years of age with a positive HPeV polymerase chain reaction (PCR) from respiratory fluid and cerebrospinal fluid (CSF) specimens who had been managed at SQUH within a period of three years (January 2017–December 2019). The exclusion criteria for the current study were children aged ≥18 years, children with asymptomatic infection and children having insufficient data in their medical records. Data on the patients' demographics, clinical details, investigation results, treatments and outcomes were obtained from the SQUH patient electronic medical records, TrakCare® (InterSystems Corporation, Cambridge, USA).

Lower respiratory tract infection (LRTI) was defined as the presence of abnormal lung examination results, new infiltrates (possible or definite) on chest radiograph or oxygen need, in conjunction with a diagnosis made by a physician at presentation.[22] Secondary bacterial pneumonia was defined as the presence of LRTI with infiltrates on chest radiograph and a physician's decision to treat the child with antibiotics for five days or more.[22] Prematurity was defined as birth which occurs before 37 completed weeks of gestation. The definitions of hypotension, tachycardia and tachypnoea were based on the reference ranges in the Pediatric Advanced Life Support (PALS) booklet. Fever was defined as an elevated temperature of ≥38˚C.

Respiratory specimens were collected by nasopharyngeal aspiration and throat or nasal swabs. Real-time multiplex PCR for respiratory and cerebrospinal viruses were used to detect HPeV nucleic acid. FTD respiratory pathogens 21 kits (Fast-Track Diagnostics, Siemens healthineers company, Luxembourg, Germany) were used to test respiratory samples for the following targets: human coronaviruses (OC43, HKU1, NL63 and 229E), HPeVs, human bocavirus, parainfluenza viruses (1, 2, 3 and 4), influenza viruses (A and B), rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus, adenovirus, enteroviruses and Mycoplasma pneumonia. HPeV can cause meningitis as well. Therefore, the CSF samples of all children with an impression of meningoencephalitis during the study period were tested for herpes simplex viruses 1 & 2, varicella zoster virus, HPeVs, enteroviruses and mumps, using the FTD Viral Meningitis kits (Fast-Track Diagnostics).

The Statistical Package for the Social Sciences (SPSS), Version 25.0 (IBM Corp., Armonk, New York, USA) was used to analyse the data collected. The Chi-square or Fisher's exact test was used to compare categorical variables. For non-normally distributed continuous variables, the Mann-Whitney U test was used. A P value of <0.05 was considered significant. Children with isolated HPeV were compared to those with co-infection with other viruses to see whether those with co-infection have a more severe disease course and subsequently a worse outcome.

Table 1: Demographic features of patients with human parechovirus infection managed at Sultan Qaboos University during the study period (N = 61)

	n (%)
Gender	
Male	44 (72)
Female	17 (28)
Governorate	
Muscat	24 (39)
Al Batinah	20 (33)
Ash Sharqiyah	9 (15)
Ad Dakhiliya	7 (12)
Dhofar	1 (2)
Nationality	
Omani	61 (100)
Non-Omani	0 (0)
Median age in months (IQR)	9 (6–15)
Site of sample	
NPA	48 (79)
Throat swab	11 (18)
Nasal swab	2 (3)
Admission	
Admitted	48 (79)
Regular ward	24 (39)
High dependency unit	17 (28)
Paediatric intensive care unit	7 (12)
Median length of hospital stay in days* (IQR)	5 (3–8)
Co-morbidities	
Premature birth	10 (16)
Asthma	7 (12)
Other atopic disease	3 (5)
Immunocompromised	6 (10)
Neurological impairment	6 (10)
Sickle cell trait	4 (7)
Congenital heart disease	3 (5)

IQR = Interquartile range; NPA = Nasopharyngeal aspirate.
**Based on the total of admitted patients (n = 48).*

Ethical approval was obtained from the Medical Research Ethics Committee of the Sultan Qaboos University in May 2020 (MREC#2109).

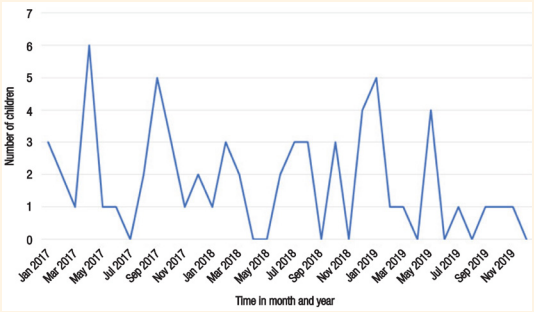

Figure 1: Monthly number of children with human parechoviruses infection from January 2017 to December 2019.

Results

Sixty-one children were managed for symptomatic HPeV infection during the study period, among whom 44 (72%) were males. All patients were of Omani nationality and had a median age of nine months (interquartile range [IQR]: 6–15 months).

The results revealed that 48 (79%) patients were hospitalised, and their median hospital length of stay was five days (IQR: 3–8 days). Twenty-four (39%) of the patients were admitted to the regular ward, while seven (12%) were admitted to the paediatric intensive care unit (PICU) for respiratory support. The most common comorbidity seen among the HPeV-infected patients was ex-prematurity [Table 1]. Eight (80%) of the preterm babies required oxygen therapy and either high dependency unit or PICU admission. Figure 1 shows that HPeV infection was detected throughout the year.

All specimens which were positive for HPeVs were respiratory specimens, majority of which were nasopharyngeal aspirates (n = 48, 79%) and throat swabs (n = 11, 18%). A lumbar puncture was not performed on any of the children because there was no suspicion of meningitis or encephalitis. HPeV PCR is part of the CSF viral multiplex PCR panel at the authors' hospital, and none of the patients who were investigated for meningitis during the study period had HPeV meningitis.

Fever (n = 41, 67%) and cough (n = 41, 67%) were the most common presenting symptoms in patients with HPeV infection in this study; seven children had rash as their presenting symptom. Two-thirds of the children with HPeVs were managed for LRTI. Gastroenteritis was not common, with only eight children having diarrhoea. HPeV PCR is not part of the gastrointestinal panel at the authors' hospital, but it was assumed that HPeV caused the diarrhoea

Table 2: Comparison of clinical, laboratory and radiological features between isolated human parechoviruses and co-infected human parechoviruses managed at Sultan Qaboos University during the study period

	n (%) or median (IQR)		*P* value	Missing
	Only parechovirus	Coinfection		
	n = 10	n = 51		
Male gender	5 (50)	39 (77)	0.12	0
Age in months	10 (6–15)	9 (6–15)	0.82	0
Weight in kg	7.6 (4.9–9.9)	8.0 (6.0–9.2)	0.85	2
Length of stay in days	7 (5–44)	5 (3–8)	0.13	13
WBC	10.3 (9.2–13.7)	12.2 (7.9–16.1)	0.85	6
ANC	3.7 (2.3–6.2)	4.7 (2.8–8.9)	0.25	6
ALC	5.6 (5.3–6.3)	4.5 (2.9–7.4)	0.66	6
Platelet	430 (279–645)	371 (279–471)	0.21	6
CRP	38.5 (9.8–86)	23 (9–58.5)	0.28	10
ALT	17.5 (10.3–21)	18.5 (15–46.3)	0.37	47
Albumin	37 (26.3–42.5)	39 (36.8–43.3)	0.30	39
Sodium	137 (135–138)	139 (136–141)	0.024	7
Creatinine	19 (17.8–25.8)	20.5 (18–23)	0.62	7
CXR infiltrates	4 (50)	26 (68)	0.42	15
Documented fever	8 (80)	33 (64.7)	0.47	0
Maximum temperature in °C	38.9 (37.8–39.4)	38.3 (37.6–39.1)	0.53	1
Lowest oxygen saturation in percentage	96 (90.3–99)	95 (89–97)	0.37	0
Tachypnoea	10 (100)	39 (78)	0.18	1
Tachycardia	4 (40)	23 (45.1)	1.0	0
Premature birth	2 (40)	8 (26.7)	0.61	26
Sickle cell	0 (0)	1 (2)	1.0	0
Preceding duration of symptoms	3.5 (2.3-4.8)	3 (1–4)	0.38	7
Nasal congestion	7 (70)	36 (70.6)	1	0
Cough	6 (60)	41 (80.4)	0.22	0
Wheezing	3 (30)	33 (64.7)	0.075	0
Retractions	4 (40)	26 (51.0)	0.731	0
Crackles/ Crepitations	4 (40)	27 (52.9)	0.51	0
Apnoea	1 (10)	3 (5.9)	0.52	0
Cyanosis	3 (30)	4 (7.8)	0.08	0
Stridor	1 (10)	5 (9.8)	1	0
Diarrhoea	1 (10)	7 (13.7)	1	0
Rash	2 (20)	5 (10)	0.32	0
LRTI	5 (50)	36 (70.6)	0.27	0
Secondary pneumonia	4 (40)	20 (39.2)	1	0
Highest level of care needed				
Admitted	9 (90)	39 (76.5)	0.67	0
PICU	1 (10)	6 (11.8)	1	0
Highest level of respiratory support needed				
Oxygen	6 (60)	21 (41.2)	0.32	0
HFNC	0 (0)	4 (7.8)	1	0
NIV	1 (10)	11 (22)	0.32	0
Invasive ventilation	0 (0)	3 (5.9)	1	0
Antibiotics	9 (90)	33 (64.7)	0.15	0
Antiviral	3 (30)	21 (41.2)	0.73	
Seizure	0 (0)	2 (3.9)	1	0
Encephalopathy	0 (0)	0 (0)	-	0
Hypotension/ Shock	0 (0)	0 (0)	-	0
Acute kidney injury	0 (0)	0 (0)	-	0
Acute liver failure	0 (0)	0 (0)	-	0
Readmission within 28 days	1 (10)	3 (5.9)	0.52	0
Chronic morbidity	0 (0)	0 (0)	-	0
Death	0 (0)	0 (0)	-	0

IQR = interquartile range; WBC = white blood cells; ANC = wbsolute neutrophil count; ALC = wbsolute lymphocyte count; CRP = c-reactive protein; ALT = alanine transaminase; CXR = chest x-ray; LRTI = lower respiratory tract infection; PICU = paediatric intensive care unit; HFNC = high-flow nasal cannula; NIV = non-invasive ventilation.

in patients with confirmed HPeV in their respiratory tract. There were no cases of meningitis or encephalitis. Tachypnoea (n = 49, 80%), tachycardia (n = 27, 44%) and wheezing (n = 36, 59%) were the most common findings on clinical examination. Apnoea, stridor and hypoxia were reported in 4 (7%), 6 (10%) and 28 (46%) children, respectively.

Co-infection with other viruses was common. A total of 51 (84%) children had a co-infection with other

viruses; of these, 34 (56%) had a co-infection with only 1 virus, 10 (16%) had a co-infection with 2 viruses, 5 (8%) had a co-infection with 3 viruses and 2 (3%) had a co-infection with 4 viruses. Rhinovirus (30, 49%) was the most common virus causing co-infection with HPeVs, followed by adenovirus (14, 23%).

Children with isolated HPeV and those co-infected with other viruses were compared. Sodium levels were lower in children with isolated HPeV (median = 137 mmol/L, IQR: 135–138 versus median = 139 mmol/L, IQR: 136–141; $P = 0.024$). Wheezing was less common among children with isolated HPeV infection compared with those with co-infection; however, this difference did not reach statistical significance ($P = 0.075$) [Table 2].

None of the patients developed sepsis, acute kidney injury or liver dysfunction. Two children (7- and 12-month-old) with HPeV infection presented with febrile seizures. All patients with HPeVs in this cohort made a full recovery. However, no long-term follow-up was done for these children, so the authors cannot comment on their neurological outcome.

Discussion

The results of this study highlight the burden of HPeV infection on the healthcare system in Oman, as the majority of the patients required hospital admission. In the current study, 44 (72%) of the HPeV-infected patients were males, which is similar to the findings of studies conducted in Iran, China and USA.[2,10,13] The median age of children who were managed for HPeV infection in the current study was nine months (IQR: 6–15 months), which is similar to an Australian study that found a median age of eight months (IQR: 6.0–11.7 months).[18] This increase in susceptibility to HPeV infection after six months of age might be due to the waning of the immunity provided by maternal antibodies.[18] The most common comorbidities seen among children with HPeVs in the current study's cohort was ex-prematurity (n = 10, 16%). Premature birth was also identified as a risk factor for HPeV infection and its complications in an Australian study.[12]

In the authors' institution, 48 (79%) of HPeV infections required hospitalisation compared to 57 (94%) RSV infections (unpublished data) which highlights the virus's burden on the healthcare facilities in Oman. Additionally, 7 (12%) of the children with HPeV infection in the current study's cohort required admission to the PICU for respiratory support, which again shows that HPeV can cause severe infection in children. An Australian study presented similar findings, with their patients having a median length of stay of 4 days (IQR: 2–13 days) and 15 (25%) of the children in their cohort requiring admission into the ICU.[7]

Viral co-infection was very common in the current study's cohort as 51 (84%) of the patients with HPeV infection had co-infection with other viruses; this is similar to what other studies have shown.[2,13,18] Rhinovirus was the most common virus causing co-infection in the current study's patients, and this agrees with the findings of two previous studies.[2,13]

HPeV infection was detected throughout the year, with a relative increase in cases in the fall and winter months. This relative increase in HPeV cases during fall and winter might be because of the opening of schools and the probability of having different HPeV genotypes circulating in Oman, which results in the different seasonality patterns. In addition, this rise might be due to the decrease in temperatures from late summer to winter. The seasonality of HPeV described in the current study is similar to what was described by Rahimi *et al.* in Iran; they found that the virus appears throughout the year without any significant differences between the various seasons.[9] The close proximity of Oman to Iran and the relatively similar weather implies that they might share similar viral genotypes. Studies in Hong Kong and Australia have shown very clear differences in infection rates between seasons compared to what has been observed in Oman.[2,7,20]

Majority of the patients with HPeVs in this study were managed for LRTI. Few (n = 8, 13%) patients had gastroenteritis, and none was managed for meningitis. This might be because of the HPeV genotype that is present in Oman. HPeV-1 causes respiratory and mild gastrointestinal infection in children, while HPeV-3 usually causes severe central nervous system infection in neonates.[2] Therefore, it is likely that HPeV-1 is the main circulating genotype in Oman since no cases of meningitis were seen among the cohort and most of the children were older than six months.

The current study suggests that HPeV infection is a benign infection in children as no mortality was reported in any of the patients, similar to what has been described recently in the USA.[13] The authors could not comment on the patients' neurological outcomes as long-term follow-up was not done.

This study has several limitations. A notable limitation is the relatively small sample size. This might be because data were collected from only one centre (SQUH) and because not all children with respiratory symptoms are tested for HPeVs, which makes it likely that there was an underestimation of the number of HPeV infections reported in the current study. As such, the results of this study may not necessarily reflect the experience in other tertiary, secondary and primary healthcare settings in Oman. Another limitation of

this study is that HPeV genotypes were not identified, making it impossible to compare the severity of infections among the different genotypes or compare the seasonal distribution of infection in Oman with that in other communities. The retrospective design of the study is another limitation since some patients had incomplete medical data. In addition, the presence of co-infection in most of the patients makes it difficult to fully attribute the clinical picture observed in them to HPeV infection. Finally, this study might not have completely assessed the burden of HPeV infections in Omani primary healthcare facilities, but the authors believe that it is a good representation of the burden of this virus among children in a tertiary healthcare setting.

Future work should include a multicentre study in Oman assessing the burden and severity of HPeV infections among children, especially neonates. Additionally, the authors recommend that studies on HPeV genotypes be conducted in order to provide a complete understanding of the burden of HPeVs in Oman healthcare facilities.

Conclusion

HPeV infection does not show a clear seasonality in Oman. Most of the infected children in the current study were <2 years of age and had a viral co-infection. The outcomes of HPeV infection were favourable, with no mortalities; however, a thorough follow-up for neurological outcomes was lacking.

AUTHORS' CONTRIBUTION

LY conceptualised the study and supervised the work. AA collected the data. ZA analysed the data. FBA and KAM interpreted the virology data. AA, FBA and KAM drafted the manuscript. ZA, FBA, KAM and LY revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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