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The Burden of Human Parechoviruses on Children in Oman

A retrospective study

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Abstract

Objectives: To study the burden, clinical and laboratory features, and outcome of Human Parechoviruses (HPeVs) infection among children managed at Sultan Qaboos University Hospital (SQUH). ***Methods:*** This is a retrospective study of children (< 18 years of age) with molecular proven HPeVinfection managed at SQUH between January 2017 and December 2019. Data was collected from patients' medical records and analyzed to describe the demographic, clinical and laboratory features, management and outcome. ***Results:*** HPeV was detected in 61 patients, 44 (72%) of whom were males. The median age of these patients was 9 months (IQR, 6-15 months). HPeV was detected throughout the year without any significant peaks. The majority of our patients (51; 84%) had co-infection with other viruses. Forty-eight (79%) children with HPeV infection required hospitalization and their median hospital length of stay was 5 days (IQR, 3 - 8 days). Ex-prematurity (10; 16%) was the most common comorbidity seen among this group. Fever (41; 67%) and cough (41; 67%) were the most common presenting symptoms among these children.Two-third of children with HPeV infection in this cohort were managed for lower respiratory tract infection and none for meningitis. Gastroenteritis was not common in our study, only 8 children had diarrhoea. All

children had a full recovery. ***Conclusion:*** HPeVs does not show a clear seasonality in Oman. Most of the children were < 2 years of age and had a viral co-infection. Outcomes of HPeVs were favorable, with no mortalities, but thorough follow-up of neurological outcomes was lacking.

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

Advances in knowledge

- The majority of children infected with HPeV were males, younger than 2 years, and had a viral co-infection.
- HPeV does not show a clear seasonality in Oman.
- No reported mortality in this group.

Application to patient care

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

Introduction

Human Parechoviruses (HPeVs) can cause gastrointestinal, severe respiratory tract, and central nervous system infections in children.[1,2] They belong to the Picornaviridae family consisting of non-enveloped positive-sense single-stranded RNA viruses[3] and are transmitted mainly by the respiratory droplets and faecal-oral routes.[4,5] There are two species of HPeVs: Parechovirus A and Parechovirus B.[6] Parechovirus A is further divided into 19 genotypes, of which HPeV-1, HPeV-3, and HPeV-6 are the most common genotypes associated with human disease.[6–8] The prevalence and seasonality of the virus differ from one place to another due to the differences in HPeV genotypes and age.[6]

HPeV infection is usually asymptomatic or associated with mild respiratory and gastrointestinal symptoms in children.[8] Some infants present with fever, irritability, and sometimes rash and they are described as "hot, red, and angry babies".[8] The less common clinical features include seizures, distended abdomen, liver failure, and pseudo-appendicitis.[8] It can also be associated with sepsis like-disease and meningoencephalitis.[7] A study from Iran

showed that HPeVs were a common cause of aseptic meningitis and sepsis like-disease compared to human enteroviruses in children less than 8 years of age between 2009 and 2011.[9] Another Iranian study reported that HPeV-1 was the main cause of diarrhea among other HPeV genotypes.[10] Zhu et al., reported in their study that HPeV infection was more common in children younger than 2 years of age.[11] Central nervous system involvement with HPeVs might result in long-term complications including white matter abnormalities, cerebral palsy, and neurodevelopmental sequelae.[6,12] Mortality from HPeV infection is rare among healthy children.[13]

HPeV infection is common across the globe and is not specific to a particular region. Australia reported 3 epidemics of HPeV-3 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 that particular area.[6] A study in Iran showed that HPeV-1 infection rates peaked during spring and autumn, while on the other hand Rahimi et al., reported that there was no significant difference in seasonality of HPeVs in Iran as it was detected throughout the year.[9,10] HPeV-1 infections appear more in the summer and autumn periods of the year in the United States, Denmark and Australia compared to Germany which showed a decrease in the 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 showed that the rates of HPeV infection in children were much higher during winter.[2,20,21]

There is limited data on the burden and outcome of HPeV infection among Omani children. Little importance has been given to HPeV infection in the Middle East region. Therefore, the results of this study will help pediatricians and healthcare professionals in Oman and in the neighboring countries to get a better understanding of the burden of this virus in the region. The aim of this study was to identify all confirmed cases of HPeV infection among children presenting to Sultan Qaboos University Hospital (SQUH), describe their clinical and laboratory features and their outcome.

Methods

This retrospective study was conducted at SQUH, one of the major tertiary care facilities in Muscat governorate, Sultanate of Oman. The study included all symptomatic children under 18 years of age managed at SQUH with a positive HPeV PCR from respiratory and

cerebrospinal fluid (CSF) specimens over a period of 3 years (January 2017 - December 2019). Exclusion criteria were age greater than or equal to 18 years, asymptomatic infection, or having insufficient data in the medical records. The patients' demographics, clinical details, investigation results, treatments, and outcomes of the infection were collected from the SQUH patient electronic medical records (TrakCare®).

Lower respiratory tract infection (LRTI) was defined as the presence of abnormal lung examination results or infiltrates (new possible or definite) seen in chest x-ray, 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 x-ray, and physician's decision to treat the child with antibiotics for 5 days or more.[22] Prematurity was defined as a birth that happens before 37 weeks of gestation. The definitions of hypotension, tachycardia and tachypnea was based on the reference ranges of the Pediatric Advanced Life Support (PALS) booklet. Fever was defined as an elevated temperature of 38°C or greater.

Respiratory specimens were collected by nasopharyngeal aspirate (NPA), throat or nasal swabs. Real-time multiplex polymerase chain reaction (real time-PCR) for respiratory and cerebrospinal viruses were used to detect HPeV nucleic acid. FTD respiratory pathogens 21 kits 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, RSV, human metapneumovirus, adenovirus, enteroviruses, and *mycoplasma pneumonia*. HPeV can cause meningitis as well. CSF samples for all children with impression of meningoencephalitis during the study period were tested for herpes simplex viruses 1 &2 (HSV 1/2), varicella zoster virus (VZV), HPeVs, enteroviruses and mumps using FTD Viral Meningitis kits.

The Statistical Package for the Social Sciences software (SPSS, version 25) was used to analyze data collected from all children who had met the inclusion criteria. To compare two categorical variables, Chi-square or Fisher's exact test was used. For non-normally distributed continuous variables, Mann-Whitney U test was used. A P-value of less than 0.05 was considered significant. Comparison was done between children with isolated HPeV and those with infection with co-viruses to see if those with co-infection have more severe disease and subsequently worse outcome.

Ethical approval was obtained from the Medical Research Ethics Committee (MREC) at the College of Medicine and Health Sciences (CoMHS) in May 2020 (MREC#2109).

Results

Sixty-one children were managed for symptomatic HPeV infection during the study period, among whom 44 (72%) children were males. All patients were of Omani nationality and the median age was 9 months (IQR, 6-15 months).

The results revealed that 48 (79%) patients were hospitalized and their median hospital length of stay was 5 days (IQR, 3-8 days). Most of these patients 24 (39%) were admitted to the regular ward while only 7 (12%) were admitted to the pediatric intensive care unit (PICU) for respiratory support. The most common comorbidity seen among HPeV infected patients was ex-prematurity as shown in table 1. Eight of the preterm babies (80%) required Oxygen therapy and either admission to high dependency or PICU admission.
Figure 1 shows that HPeV infection was detected throughout the year.

All positive specimens for HPeVs were respiratory specimens. The majority of these specimens were nasopharyngeal aspirates (48 specimens; 79%) followed by throat swabs (11 specimens; 18%). A lumbar puncture was not performed to any of these cases, as there was no suspicion of meningitis or encephalitis. HPeV PCR is part of our CSF viral multiplex PCR panel and none of the patients who were investigated for meningitis during the study period had HPeV meningitis.

Fever (41 cases, 67%) and cough (41 cases, 67%) were the most common presenting symptoms in our patients with HPeVs. Seven children had rash. Two-third of children with HPeVs were managed for LRTI. Gastroenteritis was not common; only eight children had diarrhea. HPeV PCR is not part of gastrointestinal panel in our hospital but we assumed that HPeV causes the diarrhea in patients with confirmed HPeV from respiratory tract. There were no cases of meningitis or encephalitis. Tachypnea (49 cases, 80%), tachycardia (27 cases, 44%) and wheezing (36 cases, 59%) were the most common findings on clinical examination. Apnea, stridor and hypoxia were reported in 4 (7%), 6 (10%) and 28 (46%) children respectively.

Co-infection with other viruses was common. Fifty-one children (84%) had a co-infection with other viruses including 34 (56%) with only one virus, 10 (16%) with two viruses, five (8%)

with three viruses and two (3%) with four viruses. Rhinovirus (30 cases; 49%) followed by adenovirus (14 cases; 23%) were the most common viruses causing co-infection with HPeVs.

Children with isolated HPeV and those co-infected with other viruses were compared. Sodium level was lower in children with isolated HPeV (median 137, IQR 135-138 vs 139, IQR 136-141, P = 0.024). Wheezing showed a lower frequency trend among children with isolated HPeV, however it did not reach a statistical significance (P = 0.075) as shown in table 2.

None of our patients developed sepsis, acute kidney injury or liver dysfunction. Two children (7-month and 12-month old) presented with febrile seizure during the HPeV infection. All patients with HPeVs in this cohort had full recovery. No long-term follow-up provided for these children, so we could not comment on their neurological outcome.

Discussion

The results of this study highlight the burden of HPeV infection on our health care system, as the majority needed hospital admission. In our cohort, 44 (72%) of HPeV infected patients were males which is a similar finding in studies from Iran, China and USA.[2,10,13] The median age of children managed for HPeV infection in our study was 9 months (IQR, 6-15 months) which is similar to what has been described recently by an Australian study that found a median age of 8 months (IQR, 6.0-11.7 months).[18] This increase in susceptibility to HPeV infection after 6 months of age might be due to the waning of immunity provided by maternal antibodies.[18] The most common comorbidities seen among children with HPeVs in our cohort was ex-prematurity (10; 16%). Premature birth was also identified as a risk factor for HPeV and its complications in a study from Australia.[12]

When compared to RSV infection in our institution, (48; 79%) of HPeV infections required hospitalization compared to (57; 94%) of RSV infection (unpublished data) which highlights the virus's burden on the healthcare facilities. In addition, 7 (12%) of children with HPeV in our 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 were admitted to the intensive care unit.[7]

Viral co-infection was very common in our cohort as 51 (84%) of our patients with HPeV infection have co-infection with other viruses which is similar to what other studies have shown.[2,13,18] Rhinovirus was the most common virus causing co-infection in our 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. The 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 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 our study is similar to what has been described by Rahimi et al., in Iran which showed that the virus appears throughout the year without any significant differences between the various seasons.[9] This could be because of the close proximity of Oman to Iran and relatively similar weather and might share similar viral genotypes. Studies from Hong Kong and Australia showed very clear seasonality compared to what we see in Oman.[2,7,20]

The majority of our patients with HPeVs were managed for LRTI. Few patients (8; 13%) had gastroenteritis and none were managed for meningitis. This might be because of the HPeV genotypes, which is present in Oman. HPeV-1 causes respiratory and mild gastrointestinal infection in children compared to HPeV-3 which usually causes severe central nervous system infection in neonates.[2] Therefore, it is likely that HPeV-1 is the main circulating genotype in our setting since no cases of meningitis were seen among our cohort and most of the children were older than 6 months.

Our study suggests that HPeV infection is a benign infection in children as we reported no mortality in any of our patients similar to what has been described recently in the United States.[13] We could not comment on the neurological outcomes as long-term follow-up was lacking in our cohort.

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

healthcare settings. Another limitation of this study is that HPeV genotypes were not identified and hence not possible to compare the severity of infections among the different genotypes and the seasonal distribution of infection with other communities. Furthermore, the retrospective design of the study was another limitation because some patients had incomplete medical data. In addition, presence of co-infection in most of our patients makes it difficult to make sure that the clinical picture is fully explained by HPeV infection in these patients. Finally, this study might not completely assess the burden of HPeV infections in Omani primary healthcare facilities but we believe it is a good representation of the burden of this virus among children in a tertiary healthcare setting.

Future work includes conducting a multicenter study in Oman to assess the burden of HPeV infections among children especially neonates to assess the severity. In addition, studies on HPeV genotypes are also recommended in order to have a complete understanding of the burden of HPeVs on Oman healthcare facilities.

Conclusion

HPeVs does not show a clear seasonality in Oman. Most of the children were < 2 years of age and had a viral co-infection. Outcomes of HPeVs were favorable, with no mortalities, but thorough follow-up of neurological outcomes was lacking.

Conflicts of Interest

The authors declare no conflict of interests.

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Authors' Contribution

LY conceptualized the study and supervised the work. AA collected the data. ZA analyzed 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.

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337 **Table 1: Demographic features of HPeV patients managed at Sultan Qaboos University**
338 **during the study period:**

Table 1: Demographic features of HPeV patients (N=61)	
Gender	
Male, n (%)	44 (72%)
Female, n (%)	17 (28%)
Governorate	
Muscat, n (%)	24 (39%)
Al Batinah, n (%)	20 (33%)
Ash Sharqiyah, n (%)	9 (15%)
Ad Dakhiliya, n (%)	7 (12%)
Dhofar, n (%)	1 (2%)
Nationality	
Omani, n (%)	61 (100%)
Non-Omani, n (%)	0 (0%)
Age (months)	
Median	9 months
IQR	6-15 months
Site of sample	
NPA, n (%)	48 (79%)
Throat swab, n (%)	11 (18%)
Nasal swab, n (%)	2 (3%)
Admission	
Admitted, n (%)	48 (79%)
Regular ward, n (%)	24 (39%)
High dependency unit, n (%)	17 (28%)
Paediatric intensive care unit, n(%)	7 (12%)
Length of hospital stay (days), n=48	
Median	5 days
IQR	3-8 days
Co-morbidities	

Premature birth, n (%)	10 (16%)
Asthma, n (%)	7 (12%)
Other atopic disease, n (%)	3 (5%)
Immunocompromised, n (%)	6 (10%)
Neurological impairment, n (%)	6 (10%)
Sickle cell trait, n (%)	4 (7%)
Congenital heart disease, n (%)	3 (5%)

NPA: nasopharyngeal aspirate

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

Table 2: Comparison between isolated HPeV and HPeV with coinfection

	Only Parechovirus N = 10	Coinfection N = 51	P value	Missing
Male gender, n (%)	5 (50%)	39 (77%)	0.12	0
Age, months, median (IQR)	10 (6-15)	9 (6-15)	0.82	0
Weight, kg, median (IQR)	7.6 (4.9-9.9)	8.0 (6.0-9.2)	0.85	2
Length of stay, days, median (IQR)	7 (5-44)	5 (3-8)	0.13	13
WBC, median (IQR)	10.3 (9.2-13.7)	12.2 (7.9-16.1)	0.85	6
ANC, median (IQR)	3.7 (2.3-6.2)	4.7 (2.8-8.9)	0.25	6
ALC, median (IQR)	5.6 (5.3-6.3)	4.5 (2.9-7.4)	0.66	6
Platelet, median (IQR)	430 (279-645)	371 (279-471)	0.21	6
CRP, median (IQR)	38.5 (9.8-86)	23 (9-58.5)	0.28	10
ALT, median (IQR)	17.5 (10.3-21)	18.5 (15-46.3)	0.37	47
Total Bilirubin, median (IQR)	4 (3-)	3.5 (3-5)	0.81	48
Albumin, median (IQR)	37 (26.3-42.5)	39 (36.8-43.3)	0.30	39
Sodium, median (IQR)	**137 (135-138)**	**139 (136-141)**	**0.024**	**7**
Creatinine, median (IQR)	19 (17.8-25.8)	20.5 (18-23)	0.62	7

CXR infiltrates, n (%)	4 (50%)	26 (68%)	0.42	15
Documented fever, n (%)	8 (80%)	33 (64.7%)	0.47	0
Maximum temperature, °C, median (IQR)	38.9 (37.8-39.4)	38.3 (37.6-39.1)	0.53	1
Lowest oxygen saturation, %, median (IQR)	96 (90.3-99)	95 (89-97)	0.37	0
Tachypnea, n (%)	10 (100%)	39 (78%)	0.18	1
Tachycardia, n (%)	4 (40%)	23 (45.1%)	1.0	0
Premature birth, n (%)	2 (40%)	8 (26.7%)	0.61	26
Sickle cell, n (%)	0 (0%)	1 (2%)	1.0	0
Preceding duration of symptoms, median (IQR)	3.5 (2.3-4.8)	3 (1-4)	0.38	7
Nasal congestion, n (%)	7 (70%)	36 (70.6%)	1	0
Cough, n (%)	6 (60%)	41 (80.4%)	0.22	0
Wheezing, n (%)	3 (30%)	33 (64.7%)	0.075	0
Retractions, n (%)	4 (40%)	26 (51.0%)	0.731	0
Crackles/Crepitations, n (%)	4 (40%)	27 (52.9%)	0.51	0
Apnea, n (%)	1 (10%)	3 (5.9%)	0.52	0
Cyanosis, n (%)	3 (30%)	4 (7.8%)	0.08	0
Stridor, n (%)	1 (10%)	5 (9.8%)	1	0
Diarrhea, n (%)	1 (10%)	7 (13.7%)	1	0
Rash, n (%)	2 (20%)	5 (10%)	0.32	0
LRTI, n (%)	5 (50%)	36 (70.6%)	0.27	0
Secondary pneumonia, n (%)	4 (40%)	20 (39.2%)	1	0
Highest level of care needed				
Admitted, n (%)	9 (90%)	39 (76.5%)	0.67	0
PICU, n (%)	1 (10%)	6 (11.8%)	1	0
Highest level of respiratory support needed				
Oxygen, n (%)	6 (60%)	21 (41.2%)	0.32	0
HFNC, n (%)	0 (0%)	4 (7.8%)	1	0
NIV, n (%)	1 (10%)	11 (22%)	0.32	0
Invasive ventilation, n (%)	0 (0%)	3 (5.9%)	1	0

Antibiotics, n (%)	9 (90%)	33 (64.7%)	0.15	0
Antiviral, n (%)	3 (30%)	21 (41.2%)	0.73	
Seizure, n (%)	0 (0%)	2 (3.9%)	1	0
Encephalopathy, n (%)	0 (0%)	0 (0%)	-	0
Hypotension/Shock, n (%)	0 (0%)	0 (0%)	-	0
Acute kidney injury, n (%)	0 (0%)	0 (0%)	-	0
Acute liver failure, n (%)	0 (0%)	0 (0%)	-	0
Readmission within 28 days, n (%)	1 (10%)	3 (5.9%)	0.52	0
Chronic morbidity, n (%)	0 (0%)	0 (0%)	-	0
Death, n (%)	0 (0%)	0 (0%)	-	0

Abbreviations: WBC: White blood cells; IQR: Interquartile range; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; CRP:C-reactive protein; ALT: Alanine transaminase; CXR: Chest x-ray; LRTI: Lower respiratory tract infection.

Figure 1: Monthly Number of children with HPeV infection from January 2017 to December 2019