KANSAS JOURNAL of MEDICINE

Case Report

Human Parechovirus Associated Critical Illness in Neonates and Infants: Case Series and Review of Literature

Aimee Daccache, M.D.[1], Kate Waldeck, M.D.[2], Jacob T. Kilgore, M.D., MPH[2], Mariana Lanata, M.D.[2], Robert R. Wittler, M.D.[1,3], Nisha Agasthya, M.D., FAAP[1,3]

[1]University of Kansas School of Medicine-Wichita, Wichita, KS Pediatric Residency Program

[2]Marshall University Joan C. Edwards School of Medicine, Huntington, WV

[3]Wesley Children's Hospital, Wichita, KS

Received July 29, 2023; Accepted for publication Oct. 23, 2023; Published online Nov. 30, 2023
https://doi.org/10.17161/kjm.vol16.21190

INTRODUCTION

Human Parechovirus (HPeV) is a single-stranded RNA virus belonging to the *Picornaviridae* family. Despite being initially classified as echovirus 22 and 23 among human enteroviruses due to clinical and morphological characteristics, further research has revealed that HPeV possesses unique genome organization, structure, and replication mechanisms that differentiate it from other picornavirus groups.[1] There are currently 17 known subtypes of HPeV, types 1 and 3 being the most prevalent and type 3 associated with more severe diseases.[2-4]

HPeV is known to cause respiratory and gastrointestinal illnesses. HPeV infection can be of varying illness severity, ranging from asymptomatic to severe disease including sepsis, meningitis, and in rare cases, encephalitis.[2] While most symptomatic HPeV infections are in children younger than two years, the more severe cases are often associated with neonates or infants less than three months of age.[5] A study done in Australia showed that cerebrospinal fluid (CSF) pleocytosis was absent in 96% of cases, making the diagnosis more challenging.[6] Treatment is mostly supportive care with some reported benefits of intravenous immunoglobulin (IVIg) and corticosteroid as there are no standardized treatment modalities.[7-9]

HPeV type 3 (HPeV3), the dominant genotype responsible for most severe cases, typically follows a biennial pattern, showing higher activity in even-numbered years.[10] In July 2022, the Centers for Disease Control and Prevention (CDC) issued a health advisory after receiving reports of neonates and infants with HPeV illness.[11] In this report, we describe four neonates admitted for severe HPeV illness in the summer of 2022 successfully treated with IVIg and corticosteroids.

CASE REPORT

Case 1

A six-day-old previously healthy female born at 40 weeks gestational age (GA) presented to the hospital with a temperature of 100.3°F (37.9°C), decreased responsiveness, poor latch while breastfeeding, and high-pitched crying. On hospital day two, the patient developed hypopnea associated with lateral eye deviation that was refractory to lorazepam, necessitating transfer from the pediatrics floor to the pediatric intensive care unit (PICU). The patient underwent emergent endotracheal intubation and was started on intravenous (IV) levetiracetam and phenobarbital. Seizures initially improved per continuous video electroencephalogram (cEEG), but ultimately required IV midazolam for sustained control. Full sepsis evaluation including blood, urine, and CSF studies was completed. Spinal fluid analysis demonstrated a white blood cell count of 6 cells/microL, an elevated protein of 96 mg/dL, and polymerase chain reaction (PCR) pathogen testing was positive for HPeV (Table 1). Empiric antibiotics were stopped and supportive management, including antiepileptics, was continued.

On hospital day three, the patient demonstrated symptoms of shock from the ongoing inflammatory response requiring norepinephrine, epinephrine, and hydrocortisone. On hospital day four, the patient developed intermittent subclinical seizures in the left central region despite antiepileptics. IV pentobarbital infusion was initiated to achieve burst suppression on EEG. IVIg was administered due to the ongoing hyperinflammatory state and subclinical seizures. Magnetic resonance imaging (MRI) of the brain was obtained after 24 hours of burst suppression on cEEG and showed extensive diffusion restriction involving the supratentorial juxtacortical and periventricular white matter, bilateral thalami, and corpus callosum with associated diffuse meningeal enhancement consistent with parechovirus meningoencephalitis (Figure 1).

By hospital day seven, the patient was successfully weaned from pentobarbital and continued levetiracetam and phenobarbital. She was extubated on hospital day 10 and transferred back to the pediatrics floor for continued monitoring and rehabilitation. By hospital day 17, she progressed to enteric feeds via nasogastric (NG) tube and was considered stable for discharge with close outpatient follow-up.

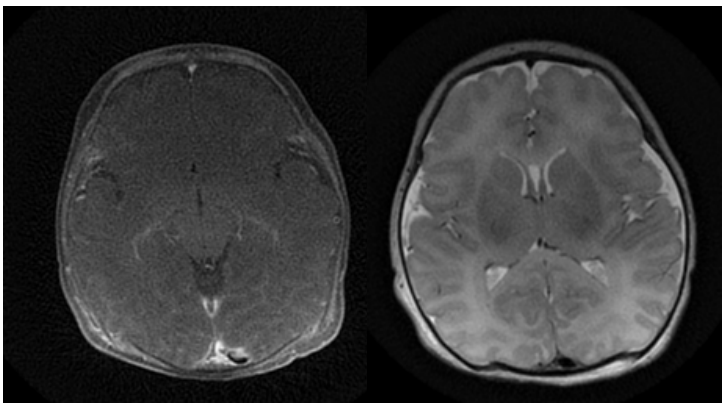

Figure 1. MRI of brain of patient 1 showing extensive diffusion restriction involving the supratentorial juxtacortical and periventricular white matter, bilateral thalami, and corpus callosum with associated diffuse meningeal enhancement.

Table 1. Demographics, presenting symptoms, and results of cerebrospinal fluid analysis.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Admission month, year	June 2022	July 2022	June 2022	August 2022
Location	Kansas	Kansas	West Virginia	West Virginia
Age, days	6	42	18	7
Gestational age, weeks	40	34	36.6	37
Sex	Female	Male	Male	Female
Race	Caucasian	Caucasian	Caucasian	Caucasian
Admission weight, kg	3.9	3.82	2.86	2.7
PRISM 3	10	15	14	16
Presenting symptoms	Fever, poor feeding	Hypothermia, poor feeding	Hypothermia, poor feeding, apnea, decreased tone	Hypothermia, poor feeding, apnea, decreased tone, erythroderma
Cerebrospinal Fluid analysis WBC, cells/microL Protein, g/dL Glucose, g/dL HPeV PCR	 6 96 63 Positive	 10 112 44 Positive	 1 71 61 Positive	 0 98 79 Positive
Complete blood count WBC, x10^3/microL Hemoglobin, g/dL Platelets, x10^3/microL Lymphocytes % Neutrophils % Monocytes % Eosinophils %	 6.3 15.0 213 8.4 82.6 7.8 0.2	 7.6 11.0 266 26.7 50.2 21.3 0.1	 8.84 16.2 248 13.4 66.0 17.5 1.0	 5.32 14.6 176 17.2 62.5 13.5 1.2
PICU admission, hospital day	2	1	2	1
Mechanical ventilation	Yes	Yes	Yes	Yes
Electrographic seizures	Yes	Yes	Yes	Asymmetric slowing
Antiepileptic medications	Lorazepam, Phenobarbital, Levetiracetam, Midazolam infusion, Pentobarbital infusion	Phenobarbital, Levetiracetam, Pentobarbital infusion	Clobazam, Fosphenytoin Levetiracetam Midazolam Oxcarbazepine, Topiramate, Pentobarbital infusion	Levetiracetam
Discharge antiepileptic medications	Phenobarbital Levetiracetam	Phenobarbital Levetiracetam	Levetiracetam Oxcarbazepine topiramate	Levetiracetam
MRI brain findings	Extensive diffusion restriction involving the bilateral supratentorial juxtacortical and periventricular white matter bilateral thalami and corpus callosum	Extensive abnormal diffusion restriction involving the periventricular and subcortical white matter as well as the corpus callosum and internal capsule patchy involvement of the bilateral thalami	Restricted diffusion within the white matter of bilateral cerebral hemispheres, the internal and external capsules, the corpus callosum, and thalami	Small foci of restricted diffusion noted within the bilateral periventricular white matter with associated mild increased signal on FLAIR imaging within the periventricular white matter
Cardiac dysfunction Vasoactives infusions BNP (pg/ml) pNT-BNP peak (pg/ml) Troponin (pg/ml)	 Epinephrine, Norepinephrine Not obtained Not obtained Not obtained	 Epinephrine, Norepinephrine, Vasopressin 768 Not obtained 913	 Epinephrine, norepinephrine Not obtained 163,964 478	 Epinephrine, Norepinephrine Not obtained 43,502 661

Table 1. Demographics, presenting symptoms, and results of cerebrospinal fluid analysis. *continued.*

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Management				
Intravenous Immunoglobulin (IVIg) dose	IVIG 1g/kg	IVIG 1g/kg	IVIG 1g/kg	IVIG 1g/kg
Steroids	Hydrocortisone 1 mg/kg every six hours	Hydrocortisone 1 mg/kg every six hours	Methylprednisolone 30 mg/kg/d	Methylprednisolone 30 mg/kg/d
Outcomes				
Ventilator days	9	7	33	13
PICU LOS, days	11	11	46	17
Hospital LOS, days	17	11	56	21
Survival to discharge	Yes	Yes	Yes	Yes
Functional State Scale	15/30	13/30	15/30	10/30
Long-term neurodevelopmental outcomes	Moderate developmental delay On Phenobarbital for seizures Diffuse hypotonia	Mild developmental delays No spasticity	Significant motor developmental delay	Normal development

Case 2

A six-week-old male born at 34 weeks GA presented to the hospital with fussiness, hypothermia, poor feeding, and episodes of stiffening at home. A full sepsis workup was done in the emergency department including a spinal fluid analysis with elevated WBC of 10 cells/microL, elevated protein 112 mg/dL, and positive HPeV on PCR panel (Table 1). Troponin I and brain natriuretic peptide (BNP) were significantly elevated, indicating signs of myocarditis (Table 1). Non-contrast computed tomography (CT) head demonstrated multiple areas of supratentorial poor gray-white matter differentiation concerning for cerebral edema (Figure 2). The patient required endotracheal intubation secondary to apnea-associated status epilepticus. cEEG revealed frequent focal sharp wave discharges from both central and temporal regions. The patient was started on IV phenobarbital and levetiracetam. In the setting of profound hemodynamic instability and shock, the patient required norepinephrine, epinephrine, and vasopressin infusions in addition to intravenous hydrocortisone. IVIg treatment was administered over 10 hours.

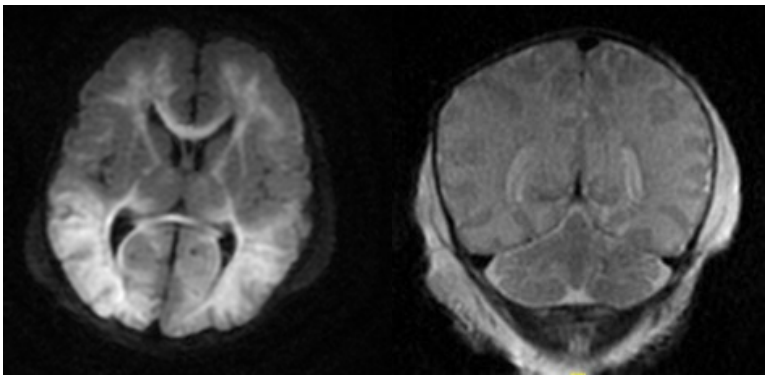

Figure 2. MRI brain of patient 2 showing extensive abnormal diffusion restriction involving the periventricular and subcortical white matter as well as the corpus callosum and internal capsule patchy involvement of the bilateral thalami.

On hospital day two, there was evidence of refractory status epilepticus. The patient was started on continuous pentobarbital infusion. CSF cultures remained negative at 48 hours, and antibiotics were discontinued. Vasopressors and pentobarbital were gradually weaned by hospital day six. MRI brain with contrast showed extensive abnormal diffusion restriction involving the periventricular and subcortical white matter, the corpus callosum, the internal capsule, and patchy involvement of the bilateral thalami (Figure 2). The patient was extubated on hospital day 7 and discharged on hospital day 11 with close outpatient follow-up.

Case 3

A previously healthy 18-day-old male born at 36.6 weeks GA was admitted for a one-day history of poor feeding, irritability, and high-pitched crying. Twelve hours after admission, the patient developed lethargy, hypothermia (95.5°F [35.3°C]), and irregular respirations with resultant respiratory acidosis requiring transfer from the pediatrics floor to the PICU. The patient was placed on bilevel-positive airway pressure (BiPAP) with an initial improvement in respiratory acidosis. A full sepsis workup was completed, and spinal fluid analysis showed no pleocytosis with normal protein and glucose, but a CSF PCR panel was positive for HPeV. On hospital day three, the patient required significant fluid resuscitation for hemodynamic instability and was intubated due to recurrent apnea. His clinical status worsened with shock and disseminated intravascular coagulation (DIC; Table 1). A transthoracic echocardiogram (TTE) revealed normal cardiac function.

cEEG showed frequent interictal subclinical seizure activity reflecting status epilepticus with seizure focus on the left frontal-temporal-central region. Seizure management included intravenous levetiracetam and then phenobarbital to achieve seizure control. A single dose of IVIg was given on hospital day four, and his EEG continued to have focal abnormalities in the left frontal-temporal-central region. pBNP levels continued to rise dramatically to over 160,000 pg/ml by day seven. A repeat TTE was obtained and was notable for mild LV dilation with low-normal left ventricular systolic function, ejection fraction of 50% suggestive of possible viral myocarditis. Given TTE findings and persistently elevated pBNP, IVIg was restarted on hospital day seven, completing a five-day course. Repeat MRI and magnetic resonance

venography (MRV) brain with contrast was notable for severely restricted diffusion in the white matter of bilateral cerebral hemispheres, the internal and external capsules, the corpus callosum, and thalami, as well as a few areas of punctate hemorrhage. On hospital day 10, cEEG demonstrated worsening bilateral epileptiform activity, and pentobarbital infusion was started to achieve burst suppression. Intravenous methylprednisolone 30 mg/kg/day burst for three days followed by a taper was also initiated. His pBNP trended down rapidly thereafter and he was weaned off pentobarbital on hospital day 18 and was seizure free on intermittent antiepileptics.

A repeat MRI brain on hospital day 22 revealed severe, widespread leukomalacia. However, the patient remained seizure-free. He was successfully extubated on hospital day 33. Ultimately, he was discharged home on hospital day 55 on levetiracetam, oxcarbazepine, and topiramate. His neurological examination at that time was non-focal.

Case 4

A previously healthy seven-day-old female born at 37 weeks GA was admitted to the PICU for hypothermia (94°F [34.4°C]), hypotonia, and apnea requiring endotracheal intubation. Sepsis workup including lumbar puncture was not pursued on admission given unstable hemodynamics and coagulopathy, but empiric antimicrobials were initiated. On hospital day two, high-dose epinephrine and norepinephrine infusions were started for ongoing hemodynamic instability. Hematologic parameters revealed DIC, and the patient received vitamin K and FFP (Table 1). pBNP (16,649 pg/ml) and troponin (661 pg/ml) were elevated, although TTE showed normal cardiac function. On hospital day four, spinal fluid analysis showed no CSF pleocytosis, but the PCR was positive for HPeV. IVIg was initiated and continued for five days. EEG normalized as starting levetiracetam.

On hospital day six, she was weaned off vasopressors, and MRI/MRV brain with contrast was obtained revealing small foci of restricted diffusion within the bilateral periventricular white matter. On hospital day seven, she had a recurrence of asymmetric, but non-epileptiform, EEG changes with an abrupt rise in pBNP and hypofibrinogenemia despite declining troponin and inflammatory markers. Given the recurrence of lateralized EEG findings correlating with known ischemia on MRI, rising pBNP, and decreasing fibrinogen, a high-dose methylprednisolone 30 mg/kg/d was started. EEG normalized on day nine. She was extubated on hospital day 14, transferred to the pediatric floor, and was able to be discharged home by hospital day 17 on levetiracetam with no focal neurological deficits.

DISCUSSION

HPeV encompasses a wide clinical spectrum with more severe presentations being noted across the U.S. in 2022.[10] We describe four neonates with severe HPeV illness presenting with seizures, sepsis, and multiorgan failure (Table 1). Studies have demonstrated that HPeV3 can cause severe sepsis-like illness, with fever, reduced feeding, neurological symptoms (such as irritability and seizures), and rash being the most frequent clinical signs observed in hospitalized children.[12-15]

According to a case series by Ristagno et al.,[16] an early diagnosis can lead to a shorter duration of hospitalization, attenuated antibiotic use, and avoidance of unnecessary diagnostic tests in critically ill infants. Therefore, timely diagnosis and intervention can provide useful prognostic guidance for families, including favorable neurologic outcomes despite illness severity.[16] While leukopenia accompanied by fever has been suggested as a distinctive characteristic of HPeV infection, there are no clinical features that can accurately differentiate HPeV3 infection from other viral or bacterial causes of sepsis in young infants. Therefore, it is necessary to have a low threshold for conducting blood and CSF testing for HPeV in acutely ill infants younger than six months. Prior research also indicates that HPeV meningoencephalitis frequently lacks CSF pleocytosis,[17,18] so an elevated white blood cell count in CSF should not be used as a criterion to determine whether HPeV testing is required. CSF analysis is necessary to confirm the diagnosis, and molecular testing such as real-time (RT)-PCR is the most sensitive and specific method for detecting HPeV in CSF.[5] Delayed diagnosis and treatment can result in severe complications, including encephalitis, hydrocephalus, and death.[19]

Unlike other forms of encephalitis and regardless of imaging results, HPeV can cause hypertension and bradycardia suggestive of possible cerebral edema.[16] HPeV3 encephalitis typically affects only the white matter. MRI imaging characteristically shows focal frontal-predominant subcortical white matter and callosal involvement with excessive high signal intensity on diffusion weight imaging. Contrastingly, neonatal HSV encephalitis typically exhibits diffuse gray and white matter changes.[16] According to a study by Midgley et al.,[20] HPeV3 can cause severe neurologic illness in neonates and, in some cases can be associated with white matter changes. They found that severe HPeV3 infections requiring critical care management were more commonly seen in infants younger than three weeks and with older infants being less critical.[20]

Focal seizures as shown by our patients are like those seen in herpes simplex virus (HSV) encephalitis. In children, a focal seizure in a specific area of the brain suggests HSV encephalitis, but in neonates, other symptoms such as generalized seizure, lethargy, and irritability may also be present.[2] In children, HSV encephalitis is commonly seen during the second or third week of life, whereas severe HPeV-A3-related disease is usually found in newborns and infants under four months of age.[2]

Currently, there are no antivirals or vaccinations for HPeV.[21] The current mainstay of treatment of neonatal enterovirus infections, including HPeV, is supportive care. Potential treatment options for HPeV infection comprise IVIg substances that inhibit the capsid, and inhibitors targeting the 3C protease.[18] The use of IVIg in treating severe diseases has been reported to have some favorable outcomes, like its use in treating severe enterovirus infections in neonates, but data are so far restricted to case reports.[7-9,21] It has been suggested that IVIg could lead to faster viral clearance due to pathogen-specific neutralizing antibodies;[8] however, the evidence is not yet definitive.[22] IVIg samples tested in Japan exhibited significant levels of neutralizing antibodies against HPeV3.[23] In laboratory tests, IVIg demonstrated a dose-dependent suppression of HPeV3 replication. Additionally, administering IVIg at an early stage proved to be more effective in reducing HPeV3 RNA levels.[9-11,22,24] Other case reports describe improvement of severe

myocarditis and dilated cardiomyopathy secondary to HPeV1 following IVIg treatment, with increased HPeV1 antibody titers being linked to the response observed.[8]

While the role of corticosteroids in bacterial meningitis is still under investigation, studies from high-income countries suggest that treatment with dexamethasone is associated with lower mortality in adults and fewer neurological and auditory sequelae in children and adults. In contrast, studies conducted in developing countries have yielded ambiguous results.[25] While studies from high-income countries suggest benefits in terms of reduced mortality and sequelae, studies in developing countries have not shown consistent results. Further research is needed to understand the factors influencing the effectiveness of corticosteroid treatment and to clarify its potential risks and benefits.[25] Our patients were successfully treated with IVIg and corticosteroids with no major neurologic deficits at discharge.

The long-term neurodevelopmental outcomes of HPeV infection have been observed to be heterogeneous, ranging from normative development to varying degrees of cognitive impairment, learning disabilities, behavioral anomalies, severe developmental delays, cerebral palsy, and intractable epilepsy.[19] In our report, patient 1 had diffuse hypotonia and moderate developmental delays at seven months old with concerns for seizures for which she is still on Phenobarbital (Table 1). Given the potential risk of neurodevelopmental abnormalities and epileptic seizures, individuals diagnosed with this condition should undergo close follow-ups with pediatric neurologists.

CONCLUSIONS

In this case series, we discuss four cases of severe illness caused by HPeV infection in neonates and young infants during the 2022 nationwide outbreak. Given the lack of antivirals at this time, prompt diagnosis and supportive management are important. In addition to typical supportive measures, IVIg and corticosteroids can be considered as adjunctive therapy in severe HPeV illness, but require more data to support routine use. Seizures can be refractory and may benefit from parental antiepileptic therapies for control. Patients are at risk for long-term neurologic sequalae and need close post-discharge follow-up. Outbreaks should be monitored with active surveillance and research focused on host immunity and anti-viral options are critical to ongoing management of severe HPeV disease, especially in neonates.

ACKNOWLEDGEMENTS

We thank the patients for allowing us to publish this report.

REFERENCES

[1] Harvala H, Wolthers KC, Simmonds P. Parechoviruses in children: Understanding a new infection. Curr Opin Infect Dis 2010; 23(3):224-230. PMID: 20414971.
[2] Aizawa Y, Izumita R, Saitoh A. Human parechovirus type 3 infection: An emerging infection in neonates and young infants. J Infect Chemother 2017; 23(7):419-426. PMID: 28511987.
[3] Benschop K, Thomas X, Serpenti C, Molenkamp R, Wolthers K. High prevalence of human parechovirus (HPeV) genotypes in the Amsterdam region and identification of specific HPeV variants by direct genotyping of stool samples. J Clin Microbiol 2008; 46(12):3965-3970. PMID: 18945833.
[4] Wolthers KC, Benschop KSM, Schinkel J, et al. Human parechoviruses as an important viral cause of sepsislike illness and meningitis in young children. Clin Infect Dis 2008; 47(3):358-363. PMID: 18558876.
[5] Kimberlin DW, Barnett ED, Lynfield R, et al. Parechovirus infections [Section 3]. Red book 2021-2024: Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2021:561-562.
[6] Khatami A, McMullan BJ, Webber M, et al. Sepsis-like disease in infants due to human parechovirus type 3 during an outbreak in Australia. Clin Infect Dis 2015; 60(2):228-236. PMID: 25301212.
[7] Yen MH, Huang YC, Chen MC, et al. Effect of intravenous immunoglobulin for neonates with severe enteroviral infections with emphasis on the timing of administration. J Clin Virol 2015; 64:92-96. PMID: 25728086.
[8] Wildenbeest JG, Wolthers KC, Straver B, Pajkrt D. Successful IVIG treatment of human parechovirus-associated dilated cardiomyopathy in an infant. Pediatrics 2013; 132(1):e243-e247. PMID: 23776125.
[9] Miura W, Momoki E, Fuchigami T, et al. Encephalitis related to human parechovirus type 3. International Journal of Clinical Pediatrics 2019; 8(2):37-40.
[10] Kadambari S, Harvala H, Simmonds P, Pollard AJ, Sadarangani M. Strategies to improve detection and management of human parechovirus infection in young infants. Lancet Infect Dis 2019; 19(2):e51-e58. PMID: 30322791.
[11] Tao L, Fill MMA, Banerjee R, Humphries RM. Notes from the field: Cluster of parechovirus central nervous system infections in young infants — Tennessee, 2022. MMWR Morb Mortal Wkly Rep 2022; 71(30):977-978. PMID: 35900934.
[12] Harvala H, Robertson I, Chieochansin T, McWilliam Leitch EC, Templeton K, Simmonds P. Specific association of human parechovirus type 3 with sepsis and fever in young infants, as identified by direct typing of cerebrospinal fluid samples. J Infect Dis 2009; 199(12):1753-1760. PMID: 19456229.
[13] Sharp J, Harrison CJ, Puckett K, et al. Characteristics of young infants in whom human parechovirus, enterovirus or neither were detected in cerebrospinal fluid during sepsis evaluations. Pediatr Infect Dis J 2013; 32(3):213-216. PMID: 23042051.
[14] Sainato R, Flanagan R, Mahlen S, Fairchok M, Braun L. Severe human parechovirus sepsis beyond the neonatal period. J Clin Virol 2011; 51(1):73-74. PMID: 21388870.
[15] Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates. Ann Neurol 2008; 64(3):266-273. PMID: 18825694.
[16] Ristagno EH, Bhalla SC, Rasmussen LK. A case series of parechovirus encephalopathy: Apnea and autonomic dysregulation in critically ill infants. J Child Neurol 2018; 33(12):788-793. PMID: 30105932.
[17] Messacar K, Breazeale G, Wei Q, Robinson CC, Dominguez SR. Epidemiology and clinical characteristics of infants with human parechovirus or human herpes virus-6 detected in cerebrospinal fluid tested for enterovirus or herpes simplex virus. J Med Virol 2015; 87(5):829-835. PMID: 25650069.
[18] De Crom SCM, Rossen JWA, van Furth AM, Obihara CC. Enterovirus and parechovirus infection in children: A brief overview. Eur J Pediatr 2016; 175(8):1023-1029. PMID: 27156106.
[19] Bucci S, Coltella L, Martini L, et al. Clinical and neurodevelopmental characteristics of enterovirus and parechovirus meningitis in neonates. Front Pediatr 2022; 10:881516. PMID: 35669403.
[20] Midgley CM, Jackson MA, Selvarangan R, et al. Severe parechovirus 3 infections in young infants—Kansas and Missouri, 2014. J Pediatric Infect Dis Soc 2018; 7(2):104-112. PMID: 28369502.
[21] Bell EJ, Grist NR. Echoviruses, carditis, and acute pleurodynia. The Lancet 1970; 295(7642):326-328. PMID: 4189581.
[22] Bauer S, Gottesman G, Sirota L, Litmanovitz I, Ashkenazi S, Levi I. Severe Coxsackie virus B infection in preterm newborns treated with pleconaril. Eur J Pediatr 2002; 161(9):491-493. PMID: 12200608.
[23] Aizawa Y, Watanabe K, Oishi T, Hirano H, Hasegawa I, Saitoh A. Role of maternal antibodies in infants with severe diseases related to human parechovirus type 31. Emerg Infect Dis 2015; 21(11):1966-1972. PMID: 26485714.
[24] Izumita R, Aizawa Y, Watanabe K, Saitoh A. A role of intravenous immunoglobulin in human parechovirus type 3 infection in an in vitro model. Open Forum Infect Dis 2016; 3(suppl_1).
[25] Borchorst S, Møller K. The role of dexamethasone in the treatment of bacterial meningitis - A systematic review. Acta Anaesthesiol Scand 2012; 56(10):1210-1221. PMID: 22524556.

Keywords: Human parechovirus, Meningoencephalitis, Intravenous Immunoglobulins, Severe Sepsis, Intravenous immunoglobulin