BRIEF REPORT

HUMAN PARECHOVIRUS MENINGOENCEPHALITIS IN AN EIGHT-DAY-OLD INFANT

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KEYWORDS

Human Parechovirus

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ABSTRACT

Human parechovirus (HPeV) infections have been increasing in the United States since May 2022, according to the Centers for Disease Control and Prevention. HPeVs are a member of the *Picornaviridae* family and share similarities with enteroviruses, though they differ in genomic structure. HPeV commonly affects children, with disease manifestations ranging anywhere from an asymptomatic infection to severe disease. HPeV typically affects the gastrointestinal and respiratory tracts but may rarely also cause severe infection of the central nervous system (CNS), leading to sepsis-like illness, meningitis, and encephalitis. Of the 19 established serotypes of HPeV, serotypes A1 and A3 are most commonly identified in humans. HPeV serotype A3 is of particular importance as it more commonly causes sepsis and CNS infection, especially in children. In the United States between 2014 and 2016, a total of 2758 cases of enteroviruses and parechoviruses were reported to the National Enterovirus Surveillance System. Of those cases, 2.3% were distinguished as HPeV A3. This case details the clinical course of an eight-day-old infant with HPeV meningoencephalitis. The infant initially presented with fever and other nonspecific symptoms, which later progressed to include diffuse erythroderma and seizure activity. Although current management of HPeV meningoencephalitis involves supportive care and close monitoring, determining HPeV as a cause of infection is important due to the long-term sequelae that patients may develop. Potential complications of infection include white matter lesions of the brain, cerebral palsy, developmental delay, and visual impairment. This case was documented to increase awareness of the rising incidence of HPeV infections in children in the United States, as well as to detail the signs and symptoms of HPeV meningoencephalitis in a neonate.

INTRODUCTION

Human parechoviruses (HPeVs) are nonenveloped positive-sense single-stranded RNA viruses with an icosahedral capsid.[1-3] They are primarily transmitted via a fecal-oral route, but may also be transmitted through the respiratory system.[2-4] They share the family Picornaviridae with enteroviruses, some well-known members including coxsackie virus, poliovirus, rhinoviruses, and hepatitis A virus, although they share no more than 30% of amino acid identity with these species.[1-4] There are currently four known species of parechoviruses: parechovirus A through D.[4,5] Parechovirus A is the only known species to infect humans, namely, "human parechovirus."[2] There are currently 19 established genotypes of HPeV, with A1 being the most common, followed by A3 and A6.[2,3]

HPeV infections range in severity from mild respiratory or gastrointestinal illness to severe systemic disease in some cases.[1,2] HPeV A1 and A6 more commonly present with mild respiratory or gastrointestinal illness, whereas HPeV A3 is more commonly implicated in severe disease, including sepsis and central nervous system (CNS) infection.[1-7] Severe HPeV infection is more often reported in young infants and tends to disproportionately affect children under 3 months of age.[2,3] CNS infection includes meningitis and encephalitis and may lead to severe sequelae including cerebral palsy, white matter lesions of the brain, visual impairment, persistent seizures, and neurodevelopmental delay.[2,3,6] In studies performed in Europe and Australia, 16%-19% of children hospitalized with severe HPeV infection showed significant concern for neurodevelopmental delay.[2] There is no currently established treatment for HPeV infection, and treatment goals involve supportive care of the respiratory and circulatory system as well as symptomatic control.[2-4]

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Intravenous immunoglobulin (IVIG), inhibition of the viral capsid, and inhibition of 3C protease may be helpful in some cases, but this has not been extensively studied thus far.[2-4]

HPeV and enterovirus infections are not subject to mandatory reporting in the United States, but the Centers for Disease Control and Prevention (CDC) established the National Enterovirus Surveillance System (NESS) in the 1960s for voluntary reporting and surveillance.[1,5] The most recent report from NESS included enterovirus and parechovirus infections in the United States from 2014-2016. Of the 2758 total infections reported during that time, 62 cases of HPeV A3 were identified, which represented 2.3% of reports.[1] HPeV A1 was reported less frequently, ranging from 1.4% of reported cases in 2015 and 2.7% in 2016.[1] Due to voluntary reporting, the true prevalence of these infections may be higher than described. In July 2022, the CDC released a health advisory alert for clinicians due to an increase in HPeV reports in multiple states since May 2022.[3]

It is important to include HPeV in the differential diagnosis for young children presenting with gastrointestinal or respiratory infections due to the recent increase in cases. It is especially important to consider this infection in young infants presenting with fever due to the potential for severe disease in this population. Most patients with systemic HPeV infection present with fever, irritability, rash, and poor feeding, which are nonspecific symptoms that share similarities with many other viral and bacterial infections.[4,7] Patients typically have low to normal white blood cell counts, normal or mildly elevated C-reactive protein, and normal liver enzymes.[4] Cerebrospinal fluid (CSF) pleocytosis is rare with HPeV CNS infection.[2,4,7] If HPeV infection is suspected, a specific polymerase chain reaction (PCR) must be performed as HPeV is not detected with nucleic acid enterovirus testing.[2,7] HPeV may be detected in stool, CSF, urine, and respiratory secretions, but stool and CSF samples are the most sensitive.[2,3] Cell culture is not sensitive for HPeV diagnosis.[3]

This case details the clinical course of an infant less than 30 days of age who developed meningoencephalitis due to HPeV infection. The infant first presented with nonspecific symptoms and a fever of unknown source. The diagnosis of HPeV meningitis was initially established following analysis of CSF and later evolved to meningoencephalitis when the infant developed focal seizure activity and diffusion abnormalities on magnetic resonance imaging (MRI).

CASE PRESENTATION

An 8-day-old female presented to her primary care physician for a new-onset fever of 101.4°F (38.6°C), decreased oral intake, and loose stools. The patient was born full term at 40 weeks and 1 day gestational age via spontaneous vaginal delivery to a group B-streptococcus–positive mother. The mother received adequate antibiotic coverage with ampicillin prior to delivery. APGAR scores at 1- and 5 minutes following delivery were documented as 8 and 9, respectively. The infant had no sick contacts, and a review of systems was negative for cough, rash, or vomiting. Physical exam findings were significant for prolonged capillary refill, jaundice, and dry mucous membranes.

The patient was admitted to the hospital for a workup of a fever in an infant. On admission, complete blood count revealed no leukocytosis (Table 1). A complete metabolic panel revealed mild hypoglycemia and increased blood urea nitrogen (BUN)/creatinine ratio but was otherwise unremarkable (Table 2). A full septic workup was performed including blood cultures, urinalysis and urine culture, and lumbar puncture including meningitis panel (Table 3, Table 4). The patient was placed on empiric intravenous ampicillin (100 mg/kg every 6 hours) and gentamicin (4 mg/kg every 24 hours), and was monitored for worsening symptoms. CSF analysis revealed normal white blood cell count, normal protein, and slightly decreased glucose (Table 3). A Biofire® Film-array® Meningitis/Encephalitis Panel performed on the patient's CSF was positive for HPeV, formally diagnosing this infant with HPeV meningitis (Table 4). On hospital day two, the patient developed diffuse blanching erythroderma (Figure 1), which is often a finding in systemic parechovirus infection. In the literature, infants with systemic parechovirus infection are said to be "red, hot, angry babies," due to fever, irritability, and rash.[2,3] The patient was monitored closely and noted to improve steadily over the course of 72 hours. The patient was afebrile during the admission and CSF, blood, and urine cultures remained negative.

TABLE 1:

Complete blood count with differential on admission showing normal hemoglobin, hematocrit, leukocyte counts, elevated RDW, and slightly elevated nRBCs.

Complete Blood Count With Differential	Patient's Values	Reference Values
WBCs	7.4	5.0-21.0 x 10*3/uL
RBCs	5.39	3.60-6.20 x 10*6/uL
Hemoglobin	18.2	12.5-20.0 g/dL
Hematocrit	53.8	39.0%-63.0 %
MCV	99.8	86.0-124.0 fL
MCH	33.7	28.0-40.0 pg
MCHC	33.8	28.0-38.0 g/dL
RDW	16.4 (high)	11.8%-15.2%
Platelets	233	141-359 x 10*3/uL
nRBC	0	0.0%-0.0 %
nRBC absolute	0.01 (high)	0.00-0.00 x 10*3/uL

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; nRBC, nucleated red blood cell; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell

TABLE 2:

Complete metabolic panel on admission showing mild hypoglycemia, elevated BUN/creatinine ratio, elevated anion gap, and low globulin

Complete Metabolic Panel	Patient's Values	Reference Values
BUN	14	5-27 mg/dL
Sodium	141	131-143 mmol/L
Potassium	5.1	3.7-5.9 mmol/L
Chloride	108	99-116 mmol/L
CO_2	17.9	16.0-28.0 mmol/L
Glucose	47 (low)	50-80 mg/dL
Creatinine	0.39	0.30-0.80 mg/dL
Calcium	9.1	9.0-10.9 mg/dL
Total protein	5.3	4.3-6.9 g/dL
Albumin	3.5	2.7-4.8 g/dL
ALT (SGPT)	20	10-32 IU/L
Alkaline phosphatase	157	60-321 IU/L
AST	63	18-63 IU/L
Total bilirubin	8.7	0.0-12.0 mg/dL
BUN/creatinine ratio	36 (high)	8-23
Osmolality calculated	279	270-350 mOsm/kg
Anion cap	15 (high)	6-13 mmol/L
Globulin	1.8 (low)	2.0-4.5 g/dL
A/G ratio	1.9	0.9-2.4
Corrected calcium	9.5	9.0-10.9 mg/dL

Abbreviations: A/G, albumin/globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood, urea, nitrogen; SGPT, serum glutamic-pyruvic transaminase

TABLE 3:

Results of CSF analysis from lumbar puncture showing normal WBC count, slightly decreased glucose, and normal protein

Cerebral-Spinal Fluid Analysis	Patient's Values	Reference Values
Color, CSF	Colorless	Clear/colorless
Number of cells, CSF	12	0-25
Red cell count	7	0-5
WBC, CSF	5	<20/mm3
Segmented neutrophils	0	<3%
Lymphocytes	36	70%
Monocytes	64	30%
Glucose, CSF	46	50-80 mg/dL
Protein, CSF	44	15-45 mg/dL

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell

TABLE 4:

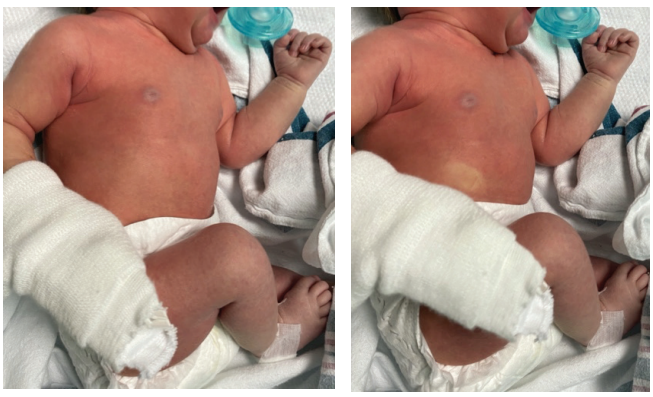
Biofire® Film-array® Meningitis/Encephalitis Panel performed on the patient's CSF, positive for HPeV

Biofire® Film-array® Meningitis/Encephalitis Panel	Patient's Values	Reference Values
Haemophilus influenzae	Not Detected	Not Detected
Escherichia coli K1	Not Detected	Not Detected
Listeria monocytogenes	Not Detected	Not Detected
Enterovirus	Not Detected	Not Detected
HSV-1	Not Detected	Not Detected
HSV-2	Not Detected	Not Detected
HHV-6	Not Detected	Not Detected
HPeV	DETECTED	Not Detected
Cryptococcus neoformans/gattii	Not Detected	Not Detected
Neisseria meningitidis	Not Detected	Not Detected
Streptococcus agalactiae	Not Detected	Not Detected
Streptococcus pneumoniae	Not Detected	Not Detected
CMV	Not Detected	Not Detected
VZV	Not Detected	Not Detected

Abbreviations: CMV, cytomegalovirus; HHV-6, human herpesvirus 6; HPeV, human parechovirus; HSV-1, herpes simplex virus 1; HSV-2, herpes simplex virus 2; VZV, varicella-zoster virus

FIGURE 1:

Blanching erythroderma rash. Infants with severe HPeV infection are often described as "red, hot, angry babies" in literature due to the triad of fever, rash, and irritability.



The patient was discharged home with return precautions but returned to the hospital later the same day due to new-onset focal clonic movement of the left arm (Figure 2A). The clonic movement evolved to include the right arm along with eye twitching and lip smacking. An electroencephalogram (EEG) was obtained, and evidence of seizure-like activity was recorded including poorly organized background low-voltage rhythms and intermittent,

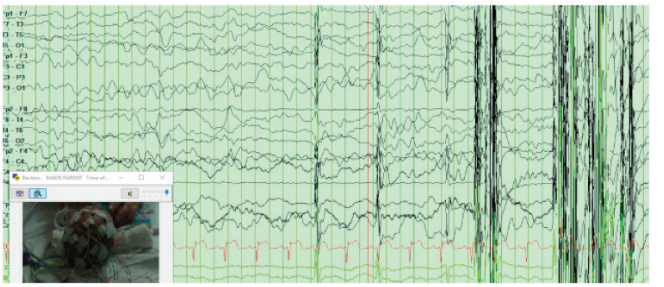
brief, generalized high-amplitude polyspike discharges with slow waves (Figure 2B). At this time, a consult was made for evaluation by pediatric neurology, who recommended controlling the seizure with a single intravenous dose of phenobarbital (20 mg/kg).

FIGURE 2A:

Video of patient experiencing focal seizure of the left arm and associated facial twitching. https://vimeo.com/764914558/7f35e523c7

FIGURE 2B:

EEG: Background rhythms consist of low-voltage poorly organized mixtures of 8 Hertz rhythms seen posteriorly with additional low-voltage 6-7 temporal theta and low- to moderate-voltage frontal 2-4 Hertz delta activity. Rhythms are generally symmetric and synchronous. Infrequent intermittent, brief, generalized high-amplitude polyspike discharges with slow waves are noted, with the image here the most active 10-second epoch. Impression: Abnormal EEG secondary to infrequent repetitive brief, generalized, high-amplitude polyspike discharges with slow waves.



Following phenobarbital administration, the patient remained in stable condition. No focal neurologic deficits were present on physical exam at that time, and she was placed on seizure precautions. A long-term EEG was performed, which revealed epileptic potential consisting of occasional sharp waves excessive for gestational age in the right central and temporal lobes. However, no clear asymmetries, focal slowing, or seizures were recorded during the study. Levetiracetam was initiated with a loading dose of 30 mg/kg orally, and the patient was continued on a maintenance dose of 40 mg/kg/day orally divided twice daily. The patient tolerated the medication well and no further seizure activity was observed during the admission.

MRI of the brain was performed showing multifocal restricted diffusion throughout the periventricular white matter of both cerebral hemispheres, with some extension into the posterior limbs of internal capsules and dorsal left thalamus (Figures 3A&B). These findings are most concerning for recent ischemia, likely due to parechovirus encephalitis. The proposed mechanism of these findings is direct neuronal injury and venous ischemia along the deep medullary veins. A magnetic resonance angiogram (MRA) of the brain was also obtained to evaluate for intracranial vascular abnormalities that may have contributed to the MRI findings. The MRA of the brain was negative for any major arterial intracranial abnormality, including saccular aneurysm, vascular nidus, or arteriovenous shunting (Figure 4A&B).

FIGURE 3A:

MRI of the brain without contrast

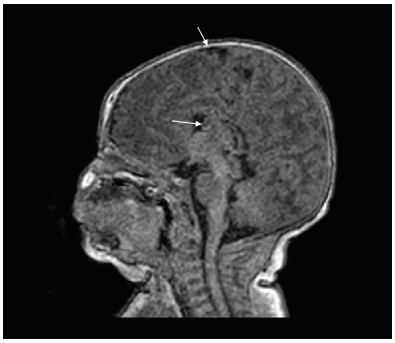


FIGURE 3B:

MRI of the brain with contrast showing multifocal diffusion restriction throughout the periventricular white matter of both cerebral hemispheres concerning for recent ischemia.

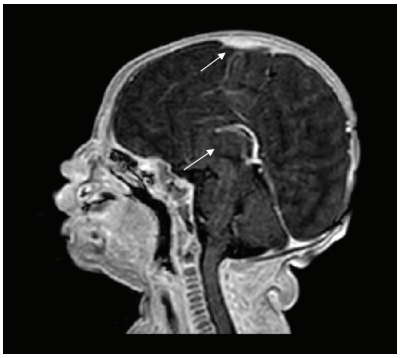


FIGURE 4A:

MRI angiogram of the brain. Image reflecting patent bilateral internal carotid arteries and basilar artery.

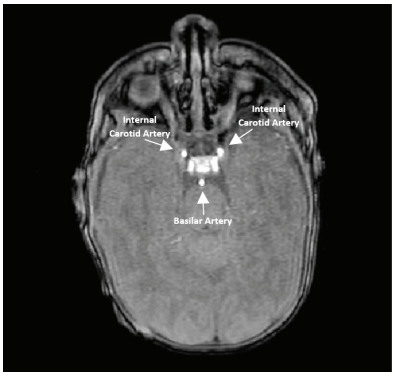
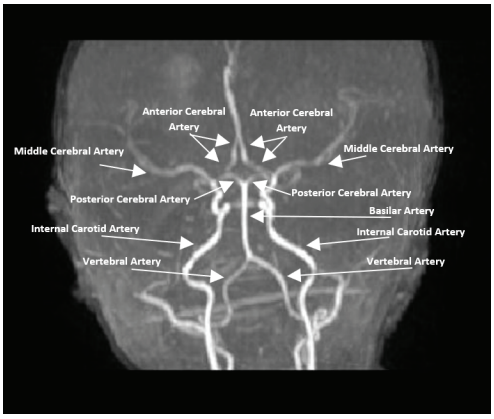


FIGURE 4B:

Patent vasculature and no evidence of major arterial intracranial abnormalities, including occlusion, aneurysm, vascular nidus, or arteriovenous shunt



The patient was discharged with parent education and strict return precautions. A follow-up with pediatric neurology was recommended 1 month following discharge for repeat EEG and medication management. The parents were also instructed to establish care with a neurodevelopmental pediatrician to closely monitor the patient's development due to the abnormal MRI findings. The follow-up examination was unremarkable for focal deficits.

DISCUSSION

HPeV infections are uncommon in the continental United States, especially those severe enough to cause CNS infection. With a recent increase in HPeV infections in the United States, it may be beneficial to include this virus in the differential diagnosis for children presenting with an acute viral illness. Although care for HPeV infection is mostly supportive, it is important to consider the potential CNS complications associated with this virus.

HPeV more commonly affects the gastrointestinal and respiratory tracts but may spread hematogenously to affect other organ systems, including the CNS. HPeV subtype A3 more commonly causes severe systemic disease when compared with other subtypes. Of the children infected with known HPeV A3, those presenting with severe systemic disease tend to be younger in age compared to those presenting with milder gastrointestinal or respiratory symptoms. Most severe cases of HPeV infection occur in infants younger than 3 months of age. This has important implications in the neurodevelopment of young children with HPeV infection and warrants close monitoring for long-term neurologic complications.

Inflammation and cytotoxicity associated with infection of the brain and spinal cord may cause irreversible neurologic damage. Infection of the CNS increases the risk of cerebral palsy, anoxic brain injury, and white matter lesion development. This may subsequently result in neurodevelopmental delay, visual impairment, delays in motor development, recurrent seizures, and even death.

CONCLUSION

Diagnosis of HPeV as the cause of infection in children is important when considering that young infants are at increased risk for severe disease. The increase in incidence of HPeV cases in the United States should encourage testing for this virus in infants less than 90 days old presenting with a fever, as well as children presenting with gastrointestinal and respiratory illnesses. Close monitoring and follow-up are important in young infants with HPeV infection and may aid in earlier detection of CNS manifestations and improve neurodevelopmental outcomes.

Literature Search and Data Sources

Literature review was performed by using Google Scholar and PubMed. Search criteria included "human parechovirus meningitis," "parechovirus encephalitis," "neonatal encephalitis," and "human parechovirus 3 outcomes." Other sources were acquired from the citations used in other publications. Dates of literature review are between October 1, 2022, and March 30, 2023.

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