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Case report

Severe human parechovirus sepsis beyond the neonatal period

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ABSTRACT

Here we describe a case of viral sepsis beyond the neonatal period caused by human parechovirus subtype 3 (HPeV-3), which manifested as cardio-respiratory failure, hepatitis, and necrotizing enterocolitis (NEC). HPeV-1 and 2 were originally classified as enteroviruses but the advent of sequence analysis led to them being recognized as a new genus in the picornavirus family. Subsequently, nine additional HPeV strains have been reported including HPeV-3 in 1999.[1] The spectrum of disease that these viruses may cause is still unknown, and they are rarely screened for in clinical practice.

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1. Case description

A previously healthy 7-week-old male presented to a military medical center in the northwest United States with chief complaint of fever to 100.9 F. Patient was fussy but consolable. He had normal intake, adequate urine output, and no signs of focal infection. He was febrile to 101.7 F, moderately dehydrated, and tachycardic to 230 beats/min; tachycardia resolved as the patient defervesced. Electrocardiogram was normal. Complete blood count (CBC) revealed mild leucopenia (4.1/μL) with normal band count and mild anemia (8.5 g/dL). Patient was admitted for routine evaluation and treated with ceftriaxone while awaiting culture results.

Over the next 24 h his fever increased to 103 F. He developed respiratory failure requiring mechanical ventilation and fluid-refractory hypotension prompting dopamine and epinephrine therapy. His physical exam and abdominal radiographs were concerning for marked abdominal distention and dilated bowel which necessitated surgical evaluation. Open laparotomy was significant for thickened, hyperemic transverse colon consistent with NEC. Initial aspartate aminotransferase (AST) was 131 units/L and alanine aminotransferase (ALT) was 71 units/L.

The patient's condition declined further over the next several days; he developed a severe coagulopathy requiring 2 fresh frozen plasma, 5 platelet, and 3 packed red blood cell transfusions. AST and ALT peaked at 4582 and 521 units/L, respectively. Vancomycin, piperacillin/tazobactam, and acyclovir were initiated. Blood, cerebrospinal fluid (CSF), urine, and stool cultures were negative. CSF white blood cell (WBC) count was 3 cells/mm^3. Tracheal aspirate grew light mixed oropharyngeal flora. Hepatitis A and C antibodies were negative as was hepatitis B surface antigen. Polymerase chain reaction (PCR) and reverse-transcriptase PCR, as applicable, were performed on plasma for EV, HPeV, and herpes simplex virus 1/2, and on nasal wash for parainfluenza virus 1–4, influenza A/B, respiratory syncytial virus, adenovirus, coronavirus, metapneumovirus, and rhinovirus at the University of Washington, Division of Virology. Quantitative RT-PCR targeting the 5′ noncoding region of HPeV RNA was present at 8,270,000 copies/mL; all other RT-PCR and PCR assays were negative. The type of the HPeV strain was determined by sequencing the complete VP-1 region of the virus from the original plasma sample according to Benschop and others and found to be HPeV-3.[2]

Piperacillin/tazobactam was discontinued on hospital day (HD) 7, and extubation was achieved on HD 8. He was discharged after 20 days, following the resumption of normal oral feeding. The infant was screened for immunodeficiency revealing normal immunoglobulin A, G, and M levels and normal quantities of T and B cells. His well child evaluation at age 19 months demonstrated normal growth and development and no obvious sequelae from this illness.

Abbreviations: HPeV, human parechovirus; EV, enterovirus; NEC, necrotizing enterocolitis.

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2. Other similar and contrasting cases in the literature

There are no other reports associating HPeV with NEC in the literature. This case illustrates that viral sepsis can mimic severe bacterial infection even outside the neonatal period, and the need to consider HPeV-3 in addition to EV as a potential etiology. Although HPeV-3 has not been reported to the Center for Disease Control during human parechovirus surveillance in the United States,[3] there were two neonatal cases of HPeV-3 induced sepsis in the US published in 2009 in Washington, D.C. One patient developed hepatitis with a peak AST > 4500 and coagulopathy requiring both vitamin K therapy and multiple blood product transfusions. The other suffered from diarrhea and meningitis.[4]

HPeV-3 has been reported to be a cause of sepsis in neonates. Retrospective studies have found an 85% seroprevalence of HPeV-3 in Japanese children entering elementary school suggesting that this serotype is commonly acquired in childhood.[5] Only recently has a real-time PCR capable of detecting HPeV-3 been developed, allowing for more accurate diagnosis of this organism.[6]

The epidemiology of disease with HPeV-3 is not yet well defined. Three cases of neonatal sepsis caused by HPeV-3 were reported in Canada in 2005. All presented with fever, a maculopapular rash, and tachypnea. Two of the patients developed thrombocytopenia over the course of their illness and all developed a leukocytosis with >60% lymphocytes.[4] A retrospective study performed on CSF samples from children <5 years old presenting with sepsis-like illness discovered that serious HPeV infections occur outside the neonatal period. Of fifteen HPeV-induced sepsis cases among infants, the median age was 4 weeks and the oldest was almost 10 weeks.[6]

3. Discussion

The little we know so far about HPeV-3 infections resembles severe cases of EV. Both viruses have been documented as causing neonatal sepsis, hepatitis, myocarditis and viral meningitis.[5–10] A prospective study of 328 neonates admitted for fever compared the course and outcomes of bacterial versus enteroviral etiologies. Sixty-two had positive bacterial cultures resulting in 1 death while 10 had positive viral cultures for EV resulting in 2 deaths.[10] While case fatality rates for EV-induced sepsis in neonates have been reported up to 40%,[10] similar data does not exist for HPeV. Verboon-Maciolek et al. recently compared the characteristics of infants with HPeV to those with EV infection and found no significant difference between mortality or sequelae but did find that infants infected with HPeV had more gastrointestinal symptoms and were more frequently diagnosed with meningoencephalitis.[7]

Diagnosis of viral infection was previously based on viral cultures, but with the advent of PCR, more rapid and specific diagnosis of viral-induced sepsis is now possible. Many clinicians are aware of EV as a cause of sepsis syndrome in infants, and EV plasma or CSF PCR is often sent in these cases. However, the EV PCR will not detect HPeV.[7,11]

Consideration of HPeV infection in infants with suspected sepsis is important. In one retrospective study, the addition of an HPeV-specific PCR led to a 31% increase in detection of a viral cause of neonatal sepsis or CNS symptoms in children aged <5 years.[6] Rapid PCR detection of EV infection has been shown to reduce both hospital stay and duration of antibiotics[6] and would likely provide the same benefits if routinely used to diagnose HPeV infection.

Our case demonstrates that the HPeV infection can be severe even beyond the neonatal period. It should be screened for in sepsis like syndromes in infants, including infants with possible NEC. Currently, there is no specific therapy for HPeV induced viral sepsis aside from supportive care. Continued vigilance defining the prevalence and disease manifestations of HPeV may promote development of targeted therapy.

Conflict of interest

The authors have no commercial or other associations that may pose a conflict of interest.

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