Parechovirus Sepsis and Meningitis in a Neonatal Intensive Care Unit

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Abstract

The majority of febrile neonates have negative bacterial cultures and presumed viral infections. During November 2014, four febrile neonates in southeastern Wisconsin required intensive care admission for human parechovirus (HPeV) infection in the blood and/or cerebral spinal fluid (CSF). Both vertical and horizontal transmission led to disease, and a variety of signs and symptoms, including tachycardia, hypotension, neutropenia, rash and irritability accompanied fever. All neonates recovered clinically, although concern for neurodevelopmental delay remains for those with meningoencephalitis. This case series describes the presentation and short-term outcomes of neonates requiring intensive care for HPeV infections.

Background

Fever in the neonate raises concern for serious bacterial infection, but viral pathogens are more common and can cause hemodynamic instability and central nervous system infection with long-term clinical sequelae. HPeV is a small RNA virus belonging to the Picornaviridae family of enteroviruses [1]. The genus contains six members, with HPeV 3 associated with neonatal infections presenting with symptoms in the central nervous system (CNS) [2]. It most often affects children under two years of age and peaks in late summer and early fall [3]. Neonatal HPeV has been identified in European and Asian outbreaks but, to the best of our knowledge, has not been reported in the literature from the United States [4,5]. In our Midwestern, 60-bed neonatal intensive care unit, four neonates were admitted for sepsis and found to have HPeV infections in November 2014. We describe their diverse presentations and clinical courses during this cluster of cases.

Case Presentation

Patient 1 is a female born at 32 weeks gestation to a febrile mother with eclampsia. Within hours of birth, she required intubation and inotropic support and developed temperature instability. Antibiotics were started after obtaining blood and CSF cultures. She required intravenous steroids for hypotension. Blood PCR was positive for HPeV, and subsequent lumbar puncture revealed HPeV in the CSF. CSF contained two nucleated cells with elevated glucose (126 mg/dL) and protein (216 mg/dL). Over her first two days of life, the total white blood cell count decreased from 7,000 to 4,600 per µL with a lymphocytic predominance and neutropenia. After two days of mechanical ventilation and three days of inotropic support, her clinical status improved. Nasopharyngeal and rectal HPeV PCRs were negative at ten days of life, and her clinical course continued as expected for a preterm infant.

Patient 2 is a female born by normal spontaneous vaginal delivery without complications at 41 weeks gestation. She presented to the emergency department with fever, irritability and poor feeding on day of life 9. She was admitted to the acute care floor and subsequently transferred to the neonatal intensive care unit for tachycardia to 220 beats per minute requiring multiple normal saline boluses. Her complete blood count was significant for lymphopenia with appropriate hematocrit and platelet count. Her CSF had elevated nucleated cells (58 per µL), elevated red blood cells (79,000 per µL), decreased glucose (38 mg/dL) and elevated protein (115 mg/dL). PCR confirmed HPeV in the blood, CSF and nasopharynx. She defervesced after 24 hours with improvement in hemodynamics. She returned to her baseline clinical status with normal enteral intake and was discharged home after three days.

Patient 3 is a male who was born at 39 weeks gestation by repeat C-section and was discharged home on day of life 3. He presented to the emergency department on day of life 25 with fever, tachycardia, poor feeding and irritability. His initial complete blood count revealed leukopenia of 5,500 cell per µL with a left shift with normal hemoglobin and platelet count. His CSF did not contain any nucleated cells or red blood cells, and protein and glucose levels in the CSF were within normal limits. Fevers persisted for three days, during which time he continued to be intermittently irritable and tachycardic. PCR of the blood and nasopharynx was positive for HPeV; there was not sufficient CSF available for viral studies. He received five days of broad spectrum antibiotics for persistent fevers. Repeat blood cultures revealed pancytopenia with platelet count of 24,000 per µL and hematocrit of 29%, and he became neutropenic with an absolute neutrophil count of 532 cells per µL. He required two platelet transfusions and one packed red blood cell transfusion during his first week of illness. Transaminases were elevated, as was his ferritin level to greater than 20,000 ng/µL, prompting a workup for hemophagocytic lymphohistiocytosis (HLH). Though he met clinical criteria, his natural killer cell activity was normal, excluding the diagnosis. His cell counts improved throughout his ten day hospitalization, and he was discharged home. He was followed closely with pancytopenia and elevated liver enzymes normalizing within two weeks of discharge.

Patient 4 is a male born at 41 weeks gestation by induced vaginal delivery. He was well until day of life 25, when he presented to the emergency department with fever, poor feeding and apparent abdominal pain. Parents noted that his older sister had a two day history of cold symptoms. His initial blood count was significant for a white blood cell...
cell count of 5,400 cells per µL with neutrophilic predominance. His electrolytes and liver function tests were within normal limits. The initial CSF sample obtained in the emergency department was insufficient for cell counts but sent for bacterial culture and viral studies. Pediatric Surgery was consulted for concern for an acute abdomen. Abdominal x-rays and ultrasound were normal, and his firm, distended abdomen improved. He required two normal saline boluses for tachycardia and poor perfusion. He had a diffuse, erythematous macular rash on his trunk that resolved with his fever. Blood, CSF and surface PCRs were obtained in the neonatal intensive care unit and were positive for HPeV. His white blood cell count downtrended to 2,800 cells per µL with a differential significant for 45% neutrophils, 5% bands and 30% lymphocytes on his second hospital day and subsequently recovered. He resumed normal feeding and defervesced on his 3rd day of illness, and he was discharged home the following day.

Discussion

HPeV is a newly recognized member of the Picornaviridae family that causes diverse severity and presentation of disease in the neonate. The patients described here experienced disease onset throughout the first month of life with one patient, a premature infant, acquiring the virus through vertical transmission. The patients were from a large geographic area without any known shared contacts. HPeV infections typically occur in the late summer and early fall, but this cluster of cases occurred in late fall. Though this is not the typical peak, there is a low level of HPeV occurrence throughout the year [4]. Viral subtyping was not available but can be used for prognostication where available. Further cases have not been reported in infants at our institution.

While initial clinical presentations were indistinguishable from bacteremia or meningitis, this series of patients demonstrates the importance of surveillance for common seasonal viruses. High, persistent fever and neutropenia were common findings, and anemia, thrombocytopenia and elevated liver enzymes occurred in one patient. Another patient experienced abdominal pain and rash, a combination which has been documented in a case series of eight infants with HPeV infection [6]. In two patients within our case series, cerebrospinal studies were positive for HPeV despite normal white blood cell counts in the CSF, which is consistent with previous reports of HPeV central nervous system infections [7]. Based on our observations in this study, a septic infant with these characteristic laboratory findings should be assessed for viral infections in the CNS during initial workup while undergoing treatment for presumptive bacterial disease.

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory condition that can be triggered by a viral infection. A single case report of HLH describes an association with human HPeV infection [8]. HLH involves the activation of macrophages, leading to a cytokine storm and potentially severe illness. In contrast to primary, or genetic, HLH, secondary HLH is acquired when a fever and a variety of other signs and symptoms, including irritability, feeding intolerance, pancytopenia, hepatitis and rash. Both vertical and horizontal transmissions result in severe disease. HPeV blood, CSF and surface PCR should be considered in febrile term and preterm neonates, especially those with negative bacterial cultures, persistent fevers, characteristic laboratory findings and septic appearance.

Central nervous system HPeV infection occurred frequently in our patients requiring intensive care. While cerebral white matter changes on MRI have been reported after HPeV encephalitis, a minority of affected patients have neurodevelopmental impairments [2]. In a study of ten infants with confirmed HPeV infection, nine infants presented with seizure, seven had fever, and six had a rash. Among those infants, cranial ultrasound and neonatal MRI confirmed white matter changes in a majority of the infants with gliosis noted on later MRI. Outcome varied in this cohort; most children had no long-term sequelae, but those who did had significant poor outcomes such as cerebral palsy, learning problems at school age, and epilepsy [7]. All neonates in our case series were referred to developmental follow-up services and imaging at a later date. The four patients described were neurologically appropriate at the time of discharge, but it is too early to determine whether central nervous system disease will affect their long-term development.

Neonatal HPeV potentially impacts the central nervous, hematologic and immunologic systems and is an important diagnostic consideration in a febrile infant. HPeV in the neonate presents with fever and a variety of other signs and symptoms, including irritability, feeding intolerance, pancytopenia, hepatitis and rash. Both vertical and horizontal transmissions result in severe disease. HPeV blood, CSF and surface PCR should be considered in febrile term and preterm neonates, especially those with negative bacterial cultures, persistent fevers, characteristic laboratory findings and septic appearance.

References