Two Cases of Sepsis-Like Illness in Infants Caused by Human Parechovirus Traced Back to Elder Siblings with Mild Gastroenteritis and Respiratory Symptoms

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Sepsis and sepsis-like illness in neonates and infants are serious emergencies. Recently, human parechovirus type 3 (HPeV-3) has been identified as a further etiologic agent of these conditions. We report two unlinked cases of infant HPeV-3 sepsis-like illness whose sources could be traced back to elder siblings with mild gastroenteritis and respiratory symptoms.

CASE REPORTS

Patient 1, a 7-day-old full-term male newborn with a birth weight of 3,750 g was admitted in August 2010 to the intensive care unit of a pediatric tertiary-care center because of his severely reduced general condition and pale skin color. A physical examination revealed tachyarrhythmia, mild hypertonia, a prolonged capillary filling time, a slightly elevated temperature (38°C), and an erythematous macular rash. A chest X-ray, a cranial ultrasound, and an electroencephalogram demonstrated no abnormalities. An abdominal ultrasound examination detected a slight increase of the amount of free fluid and a remarkably echogenic pancreas. Serum analysis showed a slightly raised C-reactive protein (CRP) level (28.3 mg/liter; normal, ≤3 mg/liter) and an elevated interleukin-6 concentration (191 pg/ml; peak, 272 pg/ml on day 2; normal, ≤15 pg/ml), and a moderately reduced platelet count (165 × 10⁹/liter; nadir, 107 × 10⁹/liter on day 6; normal, 230 × 10⁹ to 520 × 10⁹/liter) (Fig. 1). Empirical antibiotic therapy with tobramycin and piperacillin-tazobactam was initiated. Antiviral therapy with acyclovir was initiated in parallel but withdrawn because virus was negative for HSV, cytomegalovirus (CMV), measles virus, and enterovirus. All specimens except urine tested positive for human parechovirus (HPeV) by RT-PCR, as illustrated in the top panel of Fig. 1 (for the method used, see reference 1). Because virus was detected in cerebrospinal fluid, cranial magnetic resonance imaging was done but no structural abnormalities or signs of meningitis were seen. Exanthema and enanthema disappeared after 4 days. Of note, HPeV viremia remained detectable up to days 6 and 8 of hospitalization. The patient was discharged after 10 days in good clinical condition. The full genome of the virus was sequenced (7,278 nucleotides), indicating the presence of HPeV type 3 (HPeV-3) with a recombination pattern involving non-structural protein genes typical of HPeV-6 (breakpoint around nucleotide position 5150, according to the position numbering of HPeV-3 reference strain A308/99, GenBank accession no. AB084913; please note that HPeV types are defined upon their structural [capsid] gene portions; sequencing was performed using BigDye Terminator Cycle Sequencing chemistry [Applied Biosystems, Darmstadt, Germany], and the sequences of the primers used are available upon request).

Because the patient’s parents recalled mild and self-limiting gastroenteritis in their 33-month-old daughter 5 days prior to the infant’s illness, stool samples from the sibling, as well as from both parents, were tested for HPeV by RT-PCR. Both parents tested negative, but a virus (7,278 nucleotides sequenced) completely identical to that of the patient was detected in the sibling. No other viruses typically causing gastroenteritis were found.

Patient 2, an 8-week-old full-term girl, was admitted in November 2010 to the pediatric emergency unit of a local hospital because of rapid onset of fever (>39°C), tachypnea, a tight fontanelle, irritability, and severe sucking weakness. Antibiotic therapy with ampicillin and tobramycin was started. Urine analysis and bacterial culture of catheter urine and blood specimens yielded no evidence of urinary tract infection. Serum procalcitonin (0.2 μg/liter) and CRP (<0.5 mg/dl) levels were not raised, and the interleukin-6 (25 pg/ml) concentration was not significantly elevated. On the second day of hospitalization, with a rapid decline in her general condition, a cranial ultrasound was performed but showed no abnormalities. A throat wash specimen was collected and tested by PCR and RT-PCR for 16 different respiratory and enteric viruses. Positive results were obtained only for HPeV. On the third day of hospitalization, cerebrospinal fluid was obtained but tested negative for HPeV, as well as HSV, varicella-zoster virus, and enterovirus. The infant’s clinical condition and laboratory parameters improved in due course, and antibiotic therapy was discontinued. The patient was discharged on day 5. Nucleotide sequencing of the full viral genome (7,153 nucleotides) revealed an HPeV-3 strain with HPeV-4 nonstructural protein gene sequences.
portions in the middle of the genome (breakpoints in the 5' part of the 2A protein-encoding region and the border between the 3A and 3B protein-encoding regions). The virus strain was clearly different from that detected in patient 1 (nucleotide diversity between the two HPeV-3 strains, 10.4%).

The parents reported rhinitis and self-limiting gastroenteritis starting approximately 6 days before the baby's illness in the patient's 42-month-old sister. Testing of a stool sample from the sibling revealed the exact same HPeV strain (7,153 nucleotides sequenced) as in the baby, while other viruses causing gastroenteritis were absent.

To understand the relative distribution of HPeV-3 in the community from which the two cases arose and to investigate whether the HPeV-3 strains from the sibling pairs could be found in other individuals, 32 human parechoviruses detected between July 2009 and December 2011 in our laboratory were typed (17 cases of gastroenteritis, 15 cases of respiratory illness; total number of specimens tested, 1,393 [372 stool specimens and 1,021 respiratory tract specimens, mostly nasopharyngeal aspirates]; outer primers, Cap-parEcho-F and Cap-parEcho-R [2]; inner primers, VP1-parEchoF1 and VP1-parEchoR1 [3]). Only three strains were typed as HPeV-3. All three viruses clearly differed from each other and from the two strains from the sibling pairs. Twenty-five strains were typed as HPeV-1, two were typed as HPeV-4, and two were typed as HPeV-6.

Sepsis and sepsis-like illness (SLI) in neonates and infants are serious emergencies representing major causes of childhood morbidity and mortality worldwide (4). The condition is associated with a range of bacteria, including group B streptococci, Staphylococcus aureus, Escherichia coli, and Klebsiella spp. Viral etiologies include CMV, HSV, and enteroviruses. Recently, sepsis and SLI have been linked specifically to an emerging group of viruses, the human parechoviruses (HPeV; genus Parechovirus, family Picornaviridae) (5, 6). Interestingly, as many as 16 different HPeV types have been described in a short
period of time (http://www.picornaviridae.com/parechovirus/parechovirus.htm), but only one of those, HPeV-3, seems to be specifically involved in SLI (3, 7–12; for a review, see reference 13). Here we describe two unlinked cases of SLI caused by HPeV-3, whose sources in both cases could be traced back to elder siblings with mild gastroenteritis and respiratory illness. SLI was classified according to the criteria of Wolthers et al. (6).

Unambiguous tracing of HPeV transmission chains has not been achieved before, although there are some reports describing concurrent symptoms in family members of diseased children (1, 5, 14). To the best of our knowledge, this is the first report identifying such a transmission chain. However, there is a remarkable case report describing the detection of HPeV-3 in both babies of a twin pair who fell ill 3 days apart. Interestingly, the mother of the 1-month-old babies reported an episode of diarrhea at the same time as the second infant was admitted to the hospital and a stool sample from her was also positive for parechovirus. Unfortunately, typing of the maternal sample failed, impeding the proof of the authors’ hypothesis that the mother was the source of infection (15).

The cases of HPeV infection in sibling pairs of similar ages reported here emphasize the specific susceptibility of newborns and young infants to serious HPeV-3 disease. HPeV-3 is suggested to have emerged and spread very recently in the human population (1987; range, 1980 to 1992; 16), suggesting that the current generation of mothers might not have been sufficiently exposed to this virus in childhood (13). Furthermore, it was very recently shown in two individuals that, in contrast to HPeV-1 infection, HPeV-3 infection does not elicit high titers of neutralizing antibodies, resulting in only partial in vitro neutralization of HPeV-3 (17). In addition, evidence was presented that the low neutralizing capacity of an antiserum is restricted to the HPeV-3 strain that the antiserum is raised against. Thus, a lack of maternofoetal IgG protection or a limited protective effect of HPeV-3 antibodies combined with the partially impaired (innate and adaptive) immune system of newborns might explain why the same viruses caused severe disease in infants and mild courses in elder siblings. Unfortunately, we were not able to obtain blood samples from our patients and their relatives for serological tests.

The epidemiology of HPeV is often compared to that of enteroviruses, with widespread infection during the first years of life (18–20) and cocirculation of several different virus types in the population (11, 20–24). However, except for a few contrary reports (22, 25), HPeV-3 is considered a less common type in circulation (1, 20, 23, 24, 26, 27). We also detected HPeV-3 in only 9% of the HPeV-positive individuals in our small study. This particular epidemiological property might be exploitable for clinical practice and epidemiological research. Newborns and very small infants can be protected from severe disease by separation from elder siblings and other children with respiratory and enteric disease. This prevention strategy should be applied to household contacts where exposure is usually high and clinical settings. Yet, as HPeV-3 is readily detectable by RT-PCR, laboratory testing can easily, reliably identify children who serve as sources of infection. This might be of particular relevance, as children can excrete HPeV for prolonged periods of time (21). Molecular epidemiology surveys of a broader number of household contact situations should be undertaken to identify and trace more transmission chains among family members. By gathering information on intrafamily viral attack rates, the proportion of symptomatic infections, and the spectrum of diseases, a more precise calculation of the infection risk of newborns and small infants could be provided. Performance of molecular studies in combination with serology would be ideal. Whether or not children excreting HPeV-3 should be taken out of day care institutions might be worthy of discussion.

**Nucleotide sequence accession numbers.** The HPeV-3 nucleotide sequences determined in this study have been deposited in GenBank under accession numbers JX825767 (HPeV-3 strain from patient 1) and JX826607 (HPeV-3 strain from patient 2).

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**REFERENCES**


