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Severe Parechovirus 3 Infections in Young Infants—Kansas and Missouri, 2014

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Abstract

Background—Infection with parechovirus type 3 (PeV3) can cause severe neurologic and sepsis-like illness in young infants; clinical and epidemiologic descriptions have been limited. We aimed to characterize PeV3 illness and explore risk factors for acquisition in a cluster of neonatal cases at Children's Mercy Hospital in Kansas City, Missouri.

Methods—Cerebrospinal fluid specimens were obtained from infants aged <180 days who were hospitalized with sepsis-like illness or meningitis between June 1 and November 1, 2014. PeV-positive specimens were sequenced at the Centers for Disease Control and Prevention. We reviewed the medical and birth charts of the infants and performed face-to-face parent interviews. We analyzed characteristics according to infant age and intensive care admission status.

Results—We identified 35 cases of PeV infection in infants aged 5 to 56 days. Seven infants required intensive care (median age, 11 days vs 27 days among those who did not require intensive care; $P = .0044$). Six of these 7 infants had neurologic manifestations consistent with seizures, and all 6 of them were treated with acyclovir but subsequently tested negative for herpes simplex virus. Virus sequences formed 2 lineages, both of which were associated with severe illness. Half of the infants were reported to have household contacts who were ill during the week before onset. Infants aged ≤7 days at onset were more likely to have been delivered at the same hospital.

Conclusions—PeV3 can cause severe neurologic illness in neonates, and younger infants are more likely to require intensive care. PeV3 should be considered along with herpes simplex virus and other pathogens when evaluating young infants with sepsis-like illness or meningitis. More

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widespread testing for PeV3 would enable us to gain a better understanding of the clinical scope and circulation of this virus.

Keywords

human parechovirus; neonatal infections; outbreak; parechovirus; seizure; sepsis-like illness

The genus *Parechovirus* in the family *Picornaviridae* comprises 2 species, *Parechovirus A* (formerly human parechovirus) and *Parechovirus B* (formerly Ljungan virus) [1]. *Parechovirus A* infections are associated with a variety of clinical manifestations that range from asymptomatic [2] to severe and include mild respiratory illness [2], rash [3, 4], gastroenteritis [5], myocarditis [6], encephalitis [4], meningitis [7], and sepsis-like illness [7, 8]. They are thought to be very common in the community [2, 9]; most symptomatic infections occur in infants younger than 6 months [10, 11]. *Parechovirus A* has been reported in neonates as young as 2 days [12], but reports of infection in the first week of life are rare.

To date, 19 *Parechovirus A* types have been detected worldwide [1, 13, 14]; parechovirus type 1 (PeV1) and PeV3 are typically the most commonly detected virus types [9, 15, 16]. Although PeV diagnostics are not widely available in the United States, typed viruses can be reported passively to the National Enterovirus Surveillance System (NESS) [17]. During 2009 to 2013, PeV3 was the most common PeV type reported to the NESS, constituting 12.3% (223 of 1819) of all PeV and enterovirus reports [17]. Similar to enterovirus infections, central nervous system infections with PeV3 typically occur in late summer and fall [9, 18].

In August 2014, Children's Mercy Hospital in Kansas City, Missouri (CMKC), notified the Centers for Disease Control and Prevention (CDC) of young infants and neonates experiencing seizures associated with PeV meningitis; initial sequencing at the CDC identified PeV3 in cerebrospinal fluid (CSF). Although PeV3 has been associated with sepsis-like illness, meningitis, and encephalitis [18], type-specific data are limited, and the epidemiology in very young infants is not well defined. Here, we aim to describe the epidemiologic and clinical features of these PeV3 cases and to explore possible risk factors for acquisition of infection.

Patients and Methods

Case Definition

CMKC is a large pediatric tertiary referral hospital in Kansas City that serves residents of neighboring states. Since 2010 at CMKC, CSF from all infants aged <180 days with signs of meningitis or sepsis-like illness and submitted for enterovirus testing have also been routinely tested for PeV by reverse-transcriptase polymerase chain reaction (RT-PCR). For this investigation, PeV-positive specimens were subsequently typed at the CDC. We defined a case-patient as any infant aged <180 days at CMKC with CSF confirmed to be PeV3-positive according to molecular sequencing results from the CDC between June 1 and November 1, 2014.

Virologic Investigation

PeV RT-PCR—Total nucleic acid (TNA) was extracted from 200 μl of CSF or stool suspensions (diluted 1:5 in distilled water) using an easy-MAG automated nucleic acid system (BioMérieux, Durham, NC) and eluted in 55 μl of Tris-EDTA buffer. The TNA extracted from CSF was tested by a 2-step pan-PeV and pan-entero-virus real-time RT-PCR on a 7500 fast real-time PCR system (Applied Biosystems, Foster City, CA) as described previously [19]. Specimens that tested PeV positive by RT-PCR at CMKC were subsequently sent to the CDC for confirmation and typing.

Virus Typing and Phylogenetic Analysis—At the CDC, TNA was tested by a pan-PeV nested RT-PCR that targets the PeV VP1 region [20]. Complete VP1 sequences from specimens that tested positive were typed [20] and then analyzed by the neighbor-joining and maximum-likelihood methods using MEGA version 6.0 [21]. Evolutionary distances (Kimura 2-parameter method) were calculated in units of the number of base substitutions per site. Five hundred bootstrap replicates were performed. Nucleic acid and deduced amino acid genetic distances for complete VP1 nucleotide sequences were calculated from alignments produced with MegAlign (DNASTAR 12.3.1, Madison, WI).

Epidemiologic Investigation

Because this investigation was part of a public health response, it was determined to be nonresearch by the CDC and therefore not subject to CDC institutional review board review.

Medical Chart Abstraction—For each infant with PeV-positive CSF, we abstracted demographic and clinical data from the CMKC medical chart. We collected information on symptoms, treatment, clinical course, laboratory findings, and imaging results.

Birth Chart Review—Because some case-patients were aged <2 weeks at illness onset, we also performed chart abstractions at the hospital in which the infant was born. We collected information regarding the mother's medical history, labor, delivery, and follow-up and regarding the infant's delivery and neonatal care. Because our investigation included case-patients from both Kansas and Missouri, birth chart reviews were coordinated through the appropriate health department. Birth chart review was performed for all case-patients identified before August 19, 2014. For case-patients identified after this date, because of personnel availability, we abstracted data for only those who were aged <2 weeks at illness onset.

Parent Interview—We performed face-to-face structured interviews with case-patients' parents or guardians who were willing to participate. We collected information regarding the mother's peripartum period, the infant's health before hospitalization with PeV infection, and the infant's surroundings, household contacts, and visits (professional or social) in the week before illness. Interviews were coordinated through the Kansas and Missouri state health departments. For case-patients identified before August 19, 2014, family members were contacted by telephone using contact information from CMKC to establish a time and place for the face-to-face interview. We typically conducted interviews at the family home. For case-patients identified on or after August 19, 2014, because of personnel availability,

families were approached during the infant's hospitalization, and interviews were conducted on site at CMKC.

Stool Collection—To assess PeV shedding after illness, we collected soiled diapers from case-patients and from their siblings who required diapers, tested the stool for PeV by RT-PCR, and performed sequencing as described earlier. A single diaper from each case-patient was typically collected at the time of family interview, which means that the number of days between illness onset and diaper collection was different for each case.

Statistical Analyses—For medical chart abstraction of the infants' hospitalization period, we compared characteristics of infants who were admitted to the intensive care unit (ICU) with those who were not. For the assessment of characteristics of acquisition through birth chart review and parent interview, we performed basic descriptive analyses and compared infants admitted to the ICU with those who were not. Subsequently, because PeV had rarely been reported in infants in their first week of life, we also compared characteristics in case-patients ≤7 days of age at disease onset with those who were older. Differences in epidemiologic and clinical characteristics were assessed for significance using the Fisher exact or Wilcoxon rank-sum test, as appropriate. All data were analyzed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

Results

Between June 1 and November 1, 2014, 40 infants at CMKC had PeV-positive CSF. Virus typing confirmed that 35 of these 40 infants were positive for PeV3, and 1 infant was positive for PeV4. Among the 4 remaining infants, CSF from 3 infants tested negative by VP1 RT-PCR, and CSF from 1 infant tested PeV-positive by RT-PCR but no residual specimen was available for sequencing.

Epidemiologic and clinical features of the 35 case-patients with PeV3 infection are listed in Table 1; all of these infants were hospitalized. Overall, 51% (18 of 35) were male, and the median age at illness onset was 24 days (range, 5–56 days). Common symptoms included fever (>38.0°C, 91% [32 of 35]), tachycardia (77% [27 of 35]), poor feeding (77% [27 of 35]), irritability (74% [26 of 35]), mottled skin (37% [13 of 35]), and rash (26% [9 of 34]); rash descriptions varied and were frequently nonspecific but included macules and papules both centrally and on extremities. In addition, 20% (7 of 35) of the infants had neurologic manifestations, including eye deviation and limb stiffening (hereafter referred to as seizures), that were consistent with partial or generalized seizures. Peripheral blood and CSF cell counts were typical of those previously described for patients with PeV infection [11, 12, 22]; peripheral white blood cell counts were not elevated, and a lack of CSF pleocytosis was found. The median length of stay was 3 days (range, 1–18 days). No deaths were reported.

The lone PeV4-positive infant experienced fever and difficulty breathing but did not require intensive care and was discharged home after 3 days. The infant was 6 days old at illness onset.

Among the 35 infants hospitalized with PeV3 infection, 8 required oxygen and 7 were admitted to the ICU. A comparison of infants admitted to the ICU with those who were not is shown in Table 1. All infants admitted to the ICU were aged <3 weeks (median, 11 days; range, 5–18 days) and were significantly younger than infants who did not require ICU admission (median, 27 days; range, 5–56 days; $P = .0044$). Tree of the 7 infants who required ICU admission experienced difficulty breathing, and 2 of 7 had a temperature of <35°C. It should be noted that 6 of the 7 infants who required intensive care experienced seizures (as defined earlier); all 6 of them were treated with acyclovir, and CSF samples from all of them subsequently tested negative for herpes simplex virus. Magnetic resonance imaging was performed for 3 of these 6 infants, and the results were abnormal for all of them, with white matter changes noted. Electroencephalography was performed for 2 of the 6 infants; for 1 infant, cephalopathic changes consistent with severe encephalopathy were found, and for the other infant, multifocal epileptiform discharges were seen. The median length of stay in the ICU was 4 days (range, 1–17 days). Two of the 7 infants who required ICU were discharged on anticonvulsant medication.

Complete PeV3 VP1 sequences were obtained from 35 patient CSF specimens. Phylogenetic analyses of these sequences with neighbor-joining and maximum-likelihood algorithms (Figure 1) gave similar results and showed 2 PeV3 lineages cocirculating during the investigation period. The largest PeV3 lineage (found in 30 patients) shared 97.9% to 100% nucleotide identity (NT ID) (99.5%–100% amino acid identity [AA ID]), and the smaller PeV3 lineage (5 patients) shared 99.8% to 100% NT ID (100% AA ID). Genetic distances between the 2 lineages, using the 35 VP1 sequences, ranged from 94% to 95% NT ID (98.5%–99% AA ID). Case-patients who required ICU admission were infected with either lineage, as were case-patients who experienced seizures. All PeV3 VP1 sequences acquired for this study were submitted to Gen Bank and assigned accession numbers KX356610 through KX356655.

Stool specimens (n = 18) were available from 17 PeV3 case-patients after discharge from the hospital, and 8 of these specimens tested positive for PeV3 (Figure 1); all CSF–stool pairs from individual patients exhibited ≥98.8% NT ID. Most infants provided a single stool specimen, and time between disease onset and the specimen-collection date varied among the infants. All specimens collected <25 days after onset (n = 7) tested positive for PeV3. In contrast, only 1 of 11 specimens collected beyond 25 days after disease onset (collected on day 43) tested positive for PeV3; the 10 PeV3-negative specimens were collected between 27 and 73 days after disease onset. One infant provided 2 specimens, 1 on day 24 after disease onset, which tested positive for PeV3, and 1 on day 44 after onset, which tested negative.

To understand the characteristics of infants with PeV3 infection and their families, we performed birth chart reviews and parent interviews (Table 2). One of the 35 case-patients with PeV3 infection was born and resided in Texas and was excluded. Among the remaining 34 case-patients, 26 met our criteria for birth chart review, including 22 case-patients whose infection status was detected before August 19, 2014, and 4 case-patients whose infection status was detected after this date and were aged <2 weeks at onset. Twenty-two (85%) of these 26 birth chart reviews were completed. Parents of 23 (68%) of the 34 case-patients

agreed to be interviewed; the median time between illness onset and the interview date was 24 days (range, 1–74 days). Both birth chart reviews and interviews were available for 16 cases.

Birth chart reviews to explore mother and child health at delivery were unrevealing; for example, most births were uncomplicated, case-patients were not born prematurely, and the mothers were not reported as being febrile during delivery or in the week before. Parent interviews revealed that almost half of the case-patients (11 of 23) had a household contact who was ill during the week before disease onset. Ill contacts (n = 20) typically experienced symptoms representative of mild respiratory (n = 15) or gastrointestinal (n = 5) illness or had a rash (n = 2); the specific illness of 1 contact was not described. Most (21 of 23) of the infants had a household contact aged <11 years; the median age of these contacts was 3 years (range, 13 months to 10 years). Ten case-patients had a household contact aged <11 years who was ill during the week before onset. Stool specimens were available from 7 contacts of 6 case-patients. Siblings of 2 case-patients had PeV3-positive stool, and both case-patient (CSF)–sibling (stool) pairs exhibited ≥99.8% NT ID (Figure 1); 1 sibling was reported to have developed a rash after the case-patient was discharged from CMKC, and the sibling of the other case-patient reported no symptoms. For 4 of the case-patients with PeV3 infection, a family history of neurological issues was reported, including history of seizures, attention-deficit hyperactivity disorder, and multiple sclerosis; 1 of these 4 patients experienced seizures during the hospitalization for PeV3 infection.

When we compared PeV3-positive case-patients aged ≤7 days (n = 5; listed in Table 3) with older case-patients, no apparent differences were observed in the data from the birth chart reviews or parent interviews, apart from the infant's birth hospital. Four (80%) of the 5 infants whose illness onset occurred in their first week of life were born at the same hospital (hospital A) within a period of 34 days. In contrast, only 2 (10%) of 20 case-patients who were >7 days old at illness onset were delivered at hospital A. Viruses from the 4 infants delivered at hospital A were part of the larger lineage and exhibited ≥99.7% NT ID.

Discussion

We provide here a clinical and epidemiologic description of PeV3 infection in young infants and, by typing all available specimens, have provided an in-depth type-specific disease characterization. We show that PeV3 can cause severe neurologic illness in neonates and, in some cases, associated white matter changes. All infants who required intensive care became ill during their first 3 weeks of life and were significantly younger than those who were not admitted to the ICU.

Our clinical findings are consistent with data from previous PeV investigations. We found that common symptoms during PeV3 infection include fever [7, 9, 11, 12], tachycardia [11], poor feeding [7], irritability [7, 9, 11, 12], mottled skin [23], and rash [9]. Severe PeV3 infections that required intensive care management were more common in younger infants (aged <3 weeks) in our investigation, as previously reported for untyped PeV infections [7]. We also identified seizures [3, 11, 24] associated with white matter changes as an important presentation, which was observed in 7 of 34 infants (6 of 7 in the ICU). As expected, all

infants in our investigation who presented with seizures were evaluated for HSV infection and empirically treated with intravenous acyclovir. At CMKC, acyclovir treatment was stopped once the infant tested negative for HSV and positive for PeV. By comparison, CMKC detected only 1 infant (aged <30 days) with central nervous system HSV infection during the investigation period. A wider availability of diagnostics for PeV could lead to more judicious use of acyclovir in this very young and vulnerable population. Furthermore, infection outcomes vary substantially among patients with HSV and those with PeV. Unlike the potentially fatal neurologic complications of HSV infection in infants [25], most infants in our investigation who were infected with PeV3 were discharged from the hospital in healthy condition after several days. Although longer-term neurologic sequelae after PeV infection have been observed [7, 26], we did not assess long-term outcomes in this investigation. In addition, all case-patients in our investigation survived, although PeV3 infection has been associated with rare fatalities [27, 28].

Consistent with previous reports that suggested that older siblings might pose a risk for PeV exposure [29], results of our parent interviews indicated that almost half of all case-patients had ill household contacts aged <11 years. However, data from households without recognized PeV3 infection were not available for comparison. Results of previous retrospective studies have suggested that PeVs are a common source of illness in the community; PeV has been detected in 3% to 17% of CSF specimens from hospitalized infants [12, 22, 30, 31], 13% of blood specimens from infants who required intensive care for late-onset sepsis [32], 3.7% of plasma specimens from children who presented to an emergency department [33], and 16.3% of stool specimens from children who presented to a medical center [10]. Despite these high estimates, PeVs often go undetected because of mild or asymptomatic presentations [2, 34] combined with limited application of available diagnostic tests. Although data on PeV3 circulation are limited, our cases occurred mostly within the proposed PeV3 season (late summer and fall) [9, 18].

A subset of case-patients who became ill in their first week of life were of particular concern, because infection in this age group had been reported only rarely before this investigation. To explore the possibility of perinatal infection, maternal demographics and health at delivery were reviewed closely using labor and delivery charts, but this review was unrevealing. Maternal age has been suggested to be associated with severity of illness [35], but we did not detect such an association.

We noted that 4 of 5 infants aged ≤7 days at illness onset were delivered at hospital A within a similar time period. Although it was not possible to distinguish between infections acquired in the healthcare setting versus those acquired in the community, this finding supports the recently reported possibility of healthcare-associated acquisition of PeV3 infection [13]. By comparison, it has been known for some years that PeV1 (previously named echovirus 22) can be transmitted within healthcare settings and can cause respiratory [36] or gastrointestinal [37] illness.

PeVs have been detected in a variety of specimens, including those from respiratory secretions [38] and stool [2, 10, 39]. We found that the stool of PeV3 case-patients could test positive 43 days after illness onset. By comparison, in infants followed longitudinally in

previous investigations, the median duration of shedding was 51 [2] to 58 [39] days. Prolonged shedding after symptom resolution highlights the need for constant vigilance in infection-prevention and -control practices.

Phylogenetic clustering of the PeV3 VP1 sequences indicated cocirculation of 2 PeV3 strains, which differed by ≥5% NT ID, among patients treated at CMKC. Cocirculation of different PeV3 lineages had not been observed in PeV3 outbreaks previously, but it is common in large outbreaks of enterovirus disease [40]. This observation in a local PeV3 outbreak might be attributable to the large catchment area of CMKC. Severe illness was observed in both PeV3 clusters.

Our investigation was subject to several limitations. First, PeV testing is specialized, and its availability is limited. By directing testing toward CSF specimens from hospitalized infants aged <6 months, CMKC focuses on young infants and the more severe end of the clinical spectrum; therefore, the generalizability of these results is unknown. Second, parent interviews might have been subject to recall issues, especially for the families of infants who became ill earlier in the season. Last, we were not able to sequence 5 of the 40 original CSF specimens collected; the 5 infants from whom the specimens were not collected were aged ≥18 days, but no other differences were noted.

Conclusion

PeV3 should be considered alongside HSV, enteroviruses, and other pathogens as a cause of sepsis-like illness and meningitis in young infants. In addition to informing clinical management, expanded testing for PeVs might allow for a better understanding of virus circulation and disease burden.

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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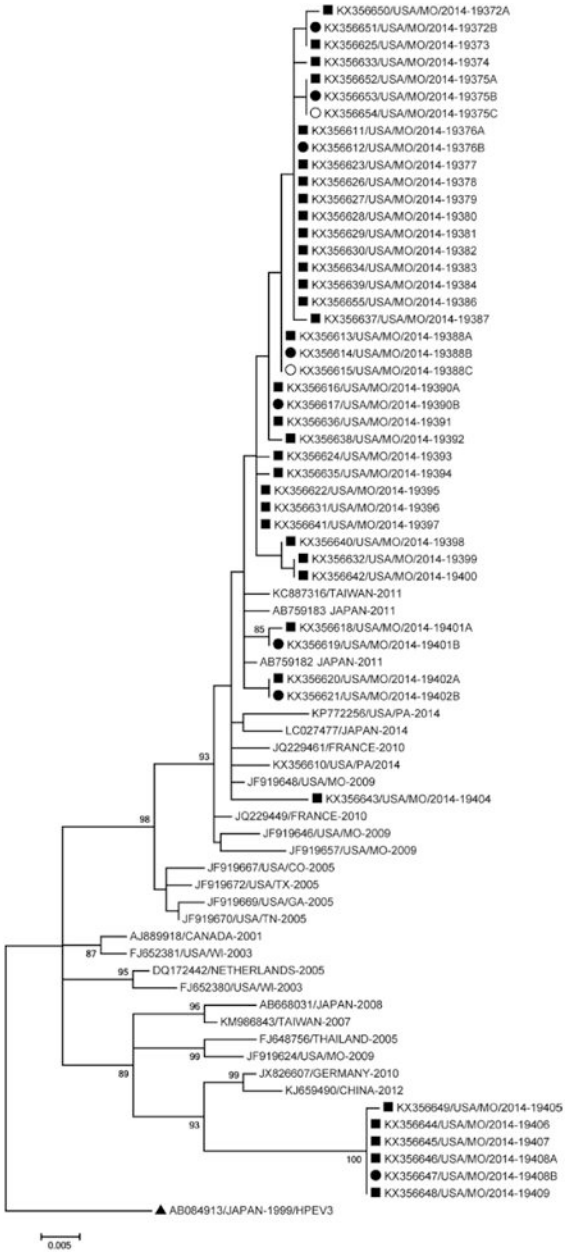

Figure 1. Maximum-likelihood phylogeny of parechovirus type 3 VP1 sequences from patients at Children's Mercy Hospital in Kansas City, Missouri, June 1 to November 1, 2014

Sequences from cerebrospinal fluid (CSF) are denoted by solid squares, from stool by solid circles, and from sibling stool by hollow circles. Single patient-associated CSF, stool, and sibling stool specimens are designated A, B, and C, respectively. Bootstrap values ≥ 80 are indicated.

Table 1

Clinical Characteristics of PeV3-Positive Case-Patients According to the Need for Intensive Care[a]

Variable	Admitted to ICU (N = 7)	Not Admitted to ICU (N = 28)	Total (N = 35)	*P* (Fisher's Exact or WRS)
Demographics				
Sex, male	4 (57)	14 (50)	18 (51)	1.0000
Infant age (days)	11 (5–18)	27 (5–56)	24 (5–56)	.0044
Febrile illness				
Fever (>38°C)	4 (57)	28 (100)	32 (91)	.0053
If fever, highest temperature (°C)	38.5–39.9	38.3–40.3	38.3–40.3	.6265
Temperature <35°C	2 (29)	0 (0)	2 (6)	.0353
Skin rash	3 (43)	6 (21)	9 (26)	.3397
Neurologic illness				
Seizures	6 (86)	1 (4)	7 (20)	<.0001
Bulging fontanelle	0 (0)	1 (4)	1 (3)	1.0000
Lethargy	1 (14)	2 (7)	3 (9)	.4525
Irritability	5 (71)	21 (75)	26 (74)	1.0000
Inconsolable crying	0 (0)	3 (11)	3 (9)	1.0000
Respiratory illness				
Cough	0 (0)	5 (18)	5 (14)	.5585
Runny nose	0 (0)	4 (14)	4 (11)	.5620
Sneezing	0 (0)	1 (4)	1 (3)	1.0000
Diffculty breathing	3 (43)	0 (0)	3 (9)	.0053
Rales/crackles/crepitations	1 (14)	0 (0)	1 (3)	.2000
Retractions/nasal faring	1 (14)	0 (0)	1 (3)	.2000
Respiratory failure	3 (43)	0 (0)	3 (9)	.0053
Cardiovascular illness				
Tachycardia	6 (86)	21 (75)	27 (77)	1.0000
If tachycardic, heart rate (beats/min)	193–200	164–225	164–225	.8376
Cyanosis	2 (29)	0 (0)	2 (6)	.0353
Mottled skin	2 (29)	11 (39)	13 (37)	.6889
Abnormal heart sounds	1 (14)	6 (21)	7 (20)	1.0000
Hypotension/shock	1 (14)	1 (4)	2 (6)	.3647
Gastrointestinal illness				
Vomiting	2 (29)	6 (21)	8 (23)	.6478
Watery stools	1 (14)	3 (11)	4 (11)	1.0000
Abdominal distention	1 (14)	5 (18)	6 (17)	1.0000
Abdominal pain	0 (0)	5 (18)	5 (14)	.5585
Jaundice	2 (29)	0 (0)	2 (6)	.0353

Variable	Admitted to ICU (N = 7)	Not Admitted to ICU (N = 28)	Total (N = 35)	*P* (Fisher's Exact or WRS)
Poor feeding	6 (86)	21 (75)	27 (77)	1.0000
Other symptoms: persistent crying	0 (0)	1 (4)	1 (3)	1.0000
Clinical course				
Oxygen given	6 (86)	2 (7)	8 (23)	<.0001
Intubated	2 (29)	0 (0)	2 (6)	.0353
Treated with acyclovir	7 (100)	9 (32)	16 (46)	.0017
Treated with antibiotics	7 (100)	27 (96)	34 (97)	1.0000
Outcome				
Length of stay (days)	9 (2–18)	3 (1–6)	3 (1–18)	.0105
ICU length of stay (days)	4 (1–17)	—	—	—
Death	0 (0)	0 (0)	0 (0)	—

Abbreviations: ICU, intensive care unit; WRS, Wilcoxon Rank Sum; PeV3, parechovirus type 3.

[a]Values shown are number (percent) or median (range). The following symptoms were collected but not reported for any infants: redness in the hands and feet, ulcers or lesions in the mouth, myoclonic jerk, tremor, limb weakness, stiff neck, cranial nerve palsy, secretions, wheezing, frothy secretions from mouth, hemoptysis, bradycardia, variable heart rate, arrhythmia, constipation, conjunctivitis, bleeding, and lymphadenopathy.

Table 2

Summary Data From Birth Chart Reviews and Family Interviews of PeV3-Positive Case-Patients

Variable	Value[a]
Birth chart review (22 performed)	
Mother's length of stay (days)	2 (2–3)
Mother's age at delivery (y)	30 (20–39)
Vaginal delivery	20/22 (91)
Scalp monitor used	1/21 (5)
Mother was febrile during delivery	0/21 (0)
Mother was febrile in the week before delivery	0/14 (0)
Mother had rash during delivery	0/21 (0)
Mother had rash in the week before delivery	1/15 (7)
Gestational age (wk)	39 (37–41)
Birth weight (kg)	3.42 (2.56–4.17)
Resuscitation required at birth	1/22 (5)
Circumcised or attempted circumcision (male, n = 14)	12/14 (86)
Infant length of stay (days)	2 (1–3)
No issues noted at discharge	21/22 (95)
Family interview (23 performed)[b]	
Mother was ill with a URI or rash during peripartum period[c]	3/23 (13)
Exclusively breastfed	15/23 (65)
Ever breastfed	20/23 (87)
History of family neurological issues	4/23 (17)
Infant on medication at home	4/23 (17)
Visited hospital before ill	0/23 (0)
Visited outpatient before ill	17/23 (74)
Infant was in daycare	0/23 (0)
Household contacts	4 (2–6)
Infant had ill household contacts	11/23 (48)
Infant had household contacts aged <11 y	21/23 (91)

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Variable	Value[a]
Infant had ill household contacts aged <11 y	10/21 (48)
Household contacts (<11 y old) in daycare or school	8/21 (38)

Abbreviations: PeV3, parechovirus type 3; URI, upper respiratory infection.

[a] Values are number/total number of infants for whom the information was known (percent) or median (range).

[b] Questions were in reference to the 1 week before the case-patient became ill with PeV3 infection.

[c] Defined here as from 1 week before delivery up to the infant's illness with PeV3 infection.

Table 3

Description of PeV3-Positive Case-Patients Who Were in Their First Week of Life at Illness Onset

Variable	Infant 1	Infant 2	Infant 3	Infant 4	Infant 5
Infant demographics					
Age at onset (days)	5	6	5	7	5
Sex	Female	Male	Female	Female	Female
Residence state	Kansas	Kansas	Missouri	Kansas	Missouri
Clinical course					
Seizure reported	No	Yes	Yes	No	No
Magnetic resonance imaging result	Abnormal	Abnormal	Abnormal	Not done	Not done
Electroencephalography result	Not done	Abnormal	Abnormal	Not done	Not done
Oxygen given	No	Yes	Yes	No	No
Intubated	No	Yes	No	No	No
Required intensive care	No	Yes	Yes	Yes	No
Treated with acyclovir	Yes	Yes	Yes	Yes	No
Treated with antibiotics	Yes	Yes	Yes	Yes	Yes
Outcome					
Length of stay (days)	6	18	9	9	4
ICU length of stay (days)	NA	17	9	7	NA
Discharged on anticonvulsant medication	No	Yes	Yes	No	No
Birth chart review					
Birth hospital	Hospital A	Hospital A	Hospital A	Hospital A	Hospital B
Mother's length of stay (days)	2	2	3	3	2
Mother's age at delivery (y)	39	38	30	28	24
Vaginal delivery	Yes	Yes	No	Yes	Yes
Scalp monitor used	No	No	No	No	No
Mother febrile during delivery	No	No	No	No	No
Mother febrile in the week before delivery	No	NR	NR	NR	No
Mother had rash during delivery	No	No	No	No	No
Mother had rash in the week before delivery	No	NR	NR	NR	No

Variable	Infant 1	Infant 2	Infant 3	Infant 4	Infant 5
Gestational age (wk)	41	39	39	39	41
Birth weight (kg)	3.81	3.83	3.32	3.13	3.59
Resuscitation required at birth	No	No	No	No	No
(Attempted) circumcision	NA	Yes	NA	NA	NA
Required NICU care at birth	No	Ye s	No	No	No
Infant's length of stay (days)	2	2	3	2	2
Issues noted at discharge	No	No	Decreased weight	No	No
Family interview[a]					
Mother was ill during peripartum period[b]	No	No	No	URI[c]	NR
Exclusively breastfed	Yes	No	Yes	Yes	NR
Ever breastfed	Yes	No	Yes	Yes	NR
History of family neurological issues	No	Yes	No	No	NR
Infant on medication at home	No	No	No	No	NR
Visited hospital before ill	No	No	No	No	NR
Visited outpatient before ill	Yes	No	Yes	Yes	NR
Infant was in daycare	No	No	No	No	NR
Household contacts	4	5	3	4	NR
Infant had ill household contacts	No	Yes	No	Yes	NR
Infant had household contacts aged <11 y	Yes	Yes	Yes	Yes	NR
Infant had ill household contacts aged <11 y	No	Yes	No	No	NR
Household contacts (<11 y old) in daycare or school	Yes	No	No	No	NR

Abbreviations: ICU, intensive care unit; NA, not available; NICU, neonatal ICU; NR, not reported; PeV3, parechovirus type 3; URI, upper respiratory infection.

[a]Questions were in reference to the 1 week before the case-patient became ill with PeV3 infection.

[b]Defined here as from 1 week before delivery up to the infant's illness with PeV3 infection.

[c]Symptoms began after delivery.