IDCases 16 (2018) xxx–xxx

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Infant identical triplets' presentation of human parechovirus Type 3

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ARTICLE INFO

Article history:
Received 14 December 2018
Received in revised form 17 January 2019
Accepted 17 January 2019

Keywords:
Parechovirus
HPeV
HPeV Type 3
Infant mortality

ABSTRACT

Introduction: Human parechovirus (HPeV) infections appear common across age groups, and transmission is likely fecal-oral and through respiratory secretions. Cyclical and seasonal patterns have been described; however, HPeV has likely been previously underdiagnosed due to lack of commercially available diagnostic testing.
Presentation of Case: We present identical triplets contracting HPeV Type 3.
Discussion: The clinical presentation, similar to echoviruses, is broad and includes asymptomatic shedding, severe pulmonary and neurologic disease, and disseminated intravascular coagulation. Neonates and young infants are particularly susceptible. In neonates, distinctive MRI brain findings have been described that, when combined with clinical presentation, suggest HPeV. Infection clusters have been described, and neonates with older siblings may be a risk factor.
Conclusion: This case suggests that HPeV has been under-recognized in the United States, and HPeV Type 3 prevalence is likely underestimated. The case highlights variation in presentation, including lack of fever and rash, which were previously documented as common HPeV symptoms.

Introduction

Human parechoviruses are picornaviridae formerly classified as echoviruses. Human parechovirus (HPeV) infections appear cosmopolitan and ubiquitous across age groups. In some populations, 85% of persons have evidence of past exposure. Transmission is likely fecal-oral and through respiratory secretions [1]. Although cyclical and seasonal patterns have been described [2], HPeV has likely been previously underdiagnosed due to lack of commercially available diagnostic testing.

Clinical presentation of HPeV, similar to other echoviruses, has a broad range including asymptomatic shedding [3], severe pulmonary [4] and neurologic disease [5], and disseminated intravascular coagulation [6]. Neonates and young infants appear particularly susceptible. In neonates, distinctive magnetic resonance imaging (MRI) brain findings have been described that, when combined with clinical presentation, suggest HPeV [7]. Infection clusters have been described [8], and neonates having older siblings has been described as a risk factor [9]. Additionally, familial transmission has been documented from asymptomatic shedding from household members [10]. We present identical triplets contracting HPeV Type 3.

Case report

A set of 4-week-old Caucasian male identical triplets with normal pregnancy, birth, and developmental history presented with extreme lethargy to the outpatient pediatrics department. They were born at 33.5-weeks gestation. After an uneventful 3 weeks in the neonatal intensive care unit, they were discharged home on the same date,10 days before presentation. The home environment included their mother, father, and 18-month-old sister. Seven days after neonatal intensive care unit discharge, they had a well-child visit. Three days after this, they presented with extreme lethargy and respiratory distress while feeding. No notable family or past medical history was recorded. There were no known ill contacts. They were admitted to the pediatric ward, then transferred to the pediatric intensive care unit and intubated within 24 h for worsening apnea.

Patient 1

Physical examination revealed a lethargic infant with diffuse hypotonia. Cardiopulmonary examination was unremarkable. He developed frequent episodes of apnea, which initially responded to

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https://doi.org/10.1016/j.idcr.2019.e00494

light stimulation but progressed in frequency and severity, requiring intubation. Within 48 h spasticity, hypertonia, and status epilepticus developed with clinical and subclinical seizures. EEG seizure pattern was multifocal with high amplitude sharp waves of 2 Hz and a background with generalized slowing. The seizures were successfully treated with fosphenytoin and levetiracetam.

Initial laboratory evaluation revealed leukopenia and mildly elevated immature granulocytes. Blood, urine, respiratory, and cerebrospinal fluid (CSF) bacterial cultures, were negative. The CSF nucleated cell count was 1/mm^3, predominantly monocytes, and protein was 68 g/dl. Respiratory viral testing by polymerase chain reaction (PCR), including enterovirus, was negative. CSF herpes simplex virus and enterovirus PCR were negative. Nasopharyngeal swab for pertussis PCR was negative. Electrocardiogram and echocardiogram were normal.

Due to severe hypotonia and rapidly progressive symptoms, he received human botulism immune globulin intravenously while awaiting stool culture results, which were ultimately negative. Carboxyhemoglobin level was elevated. Laboratory testing methods could not correct for fetal hemoglobin, and repeated evaluation of the home did not detect carbon monoxide.

Metabolic evaluation was normal, including lactate in whole blood and CSF, pyruvate, ammonia, and peroxisomal panel; plasma and CSF amino acids were normal. CSF neurotransmitters were normal, although CSF neopterin and tetrahydrobiopterin were suggestive of inflammation. Free and esterified fractions of carnitine were low, but acylcarnitines and urine C5-DC acylcarnitines were normal. Carnitine supplementation was given until carnitine levels could be reassessed and were found to be normal. Urine acylglycines, S-sulfocysteine, and urine organic acids were normal. Anti-acetylcholine receptor binding, modulating, and blocking antibodies and acetylcholine receptor muscle binding antibody were normal. Anti-MuSK antibody was negative.

Head ultrasound on admission was unremarkable, but MRI done within 36 h of admission revealed extensive deep white and basal ganglia involvement consistent with hypoxic ischemic injury. MR spectroscopy was performed with repeat images obtained one week later, which revealed findings consistent with an ischemia diagnosis.

Viral cultures of stool and respiratory secretions were obtained within 48 h of presentation and were negative. HPeV was detected by PCR from initial CSF sample at Children's Mercy Hospitals (Kansas City, MO), and was further characterized as HPeV type 3 by the (U.S.) Centers for Disease Control and Prevention.

Patient 2

Physical examination revealed similar findings to patient 1, though initially less severe. Within 24 h, he also had severe hypotonia and required intubation for frequent apnea. He underwent evaluation and treatment for botulism, other infectious etiologies, metabolic evaluation, and Anti-MuSK antibody work-up. Electrocardiogram and echocardiogram were normal. He developed hypertonia with the same timeframe and required treatment for status epilepticus with similar clinical and EEG findings. MRI within 36 h of admission showed similar findings to patient 1, but with more extensive gray matter involvement.

His course was complicated by an episode of emesis on day 7 of intubation, when his endotracheal tube was dislodged. He had desaturation and brief bradycardia with chest compressions given for approximately 40 s. Desaturation and bradycardia resolved immediately upon initiation of bag valve mask ventilation.

All viral PCR and culture testing was negative. He did not have CSF testing, but was presumed to have HPeV, given the same presentation of his identical triplet brother.

Patient 3

Physical examination of patient 3 also revealed progressive hypotonia and apnea, requiring intubation followed by development of spasticity and epileptogenicity on EEG. He underwent the same testing and treatment as his brothers, with the exception of CSF testing. His stool and respiratory viral cultures and PCRs were negative. As with patient 2, CSF was not tested for HPeV, but was presumed positive.

Follow-up

All three patients relearned drinking and breathing coordination in the following weeks. Making appropriate daily weight gains, all three were discharged on day 61. At age 36-months, developmental and physical delays were evident in two of the three boys, each with unique challenges. Patient 1 was diagnosed with left-sided cerebral palsy, significant cortical vision impairment, and developmental delays. Patient 2 was diagnosed with cortical vision impairment, spasticity, and developmental delays. Patient 3 has progressed neurotypically through the first 3 years of development and is in line with peers on all physical and cognitive aspects.

Discussion

This report describes what is, to our knowledge, a unique cluster of identical triplets with severe neurologic impairment due to HPeV infection. That all three infants fell ill after initial discharge home highlights that this was most likely a post-natal exposure, likely community, rather than a perinatal exposure. Key features in the presentation of these infants should alert the clinician to consider HPeV as a diagnosis: sepsis-like or primary neurologic presentation, characteristic magnetic resonance imaging findings including diffusion weighted changes of white matter, and unexplained neurologic syndrome without CSF pleocytosis. Commercial assays are now available to test for HPeV in CSF, but routine availability depends on local resources.

In neonates, central nervous system HPeV infection can have major sequelae lasting into childhood [11,12]. Neurologic damage mechanisms and determinants of susceptibility to severe infection are only now being unraveled. Meninges infection and possible vascular compromise may be a mechanism of injury in fatal cases [13]. Additionally, immune response may play a role in illness severity.

Conclusions

Delayed diagnosis in this case series suggests that HPeV has been under-recognized in the United States, and prevalence of HPeV Type 3 is likely underestimated. The case also highlights variation in presentation, including lack of fever and rash, which were previously documented as common symptoms [5]. Neonates with severe neurologic infections are at higher risk to develop physical disability, and close monitoring of developmental outcomes is warranted.

Further research is needed to understand prevention strategies, prevalence, treatment options, early intervention effectiveness, individual susceptibility to severe infection, mechanisms of neurologic damage, long-term outcome variation, and sequelae of severe neurologic, pulmonary, or systemic infection.

Author contributions

All authors participated in the conception or design of the work; the acquisition, analysis, or interpretation of data for the work;

drafting the work and revising it critically for important intellectual content; final approval of the version to be submitted/published; and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding sources

The authors declare they have no funding sources to acknowledge.

Ethical approval and informed consent

The authors declare that ethical approval was not required for this case report as it is not considered research; however, consent to publish was granted by the parents of the patients.

Conflict of interest disclosure

The authors have no personal or financial competing interests to disclose.

Acknowledgements

The authors would like to thank Marie Fleisner from the Marshfield Clinic Research Institute's Office of Research Support for assistance with editing the manuscript.

References

[1] Romero JR. Selvarangan r the human parechoviruses: an overview. Adv Pediatr 2011;58:65–85, doi:http://dx.doi.org/10.1016/j.yapd.2011.03.008.
[2] Esposito S, Rahamat-Langendoen J, Ascolese B, Senatore L, Castellazzi L, Niesters HG. Pediatric parechovirus infections. J Clin Virol 2014;60:84–9, doi:http://dx.doi.org/10.1016/j.jcv.2014.03.003.
[3] Wildenbeest JG, Benschop KS, Bouma-de Jongh S, Wolthers KS, Pajkrt D. Prolonged shedding of human parechovirus in feces of young children after symptomatic infection. Pediatr Infect Dis 2016;35:580–3, doi:http://dx.doi.org/10.1097/INF.0000000000001082.
[4] Vidal LRR, Cavalli B, Almeida SM, Raboni SM, Nogueira MB. Human parechovirus: sepsis-like illness with pulmonary infection. Braz J Infect Dis 2017;21:675–7, doi:http://dx.doi.org/10.1016/j.bjid.2017.06.004.
[5] Selvarangan R, Masha Nzabi, Selvaraju S, Ketter P, Carpenter C, Harrison CJ. Human parechovirus 3 causing sepsis-like illness in children from midwestern United States. Pediatr Infect Dis J 2011;30(3):238–42, doi:http://dx.doi.org/10.1097/INF.0b013e3181fbefc8.
[6] Vergnano S, Kadambari S, Whalley K, Menson EN, Martinez-Alier N, Cooper M, et al. Characteristics and outcomes of human parechovirus infection in infants (2008-2012). Eur J Pediatr 2015;174:919–24, doi:http://dx.doi.org/10.1007/s00431-014-2483-3.
[7] Amarnath C, Helen Mary T, Periakarupan A, Gopinathan K, Philson J. Neonatal parechovirus leucoencephalitis- radiological pattern mimicking hypoxic-ischemic encephalopathy. Eur J Radiol 2016;85:428–34, doi:http://dx.doi.org/10.1016/j.ejrad.2015.11.038.
[8] Tang JW, Holmes CW, Elsanousi FA, Patel A, Adam F, Speight R, et al. Cluster of human parechovirus infections as the predominant cause of sepsis in neonates and infants, Leicester, United Kingdom, 8 May to 2 August 2016. Euro Surveill 2016;21(34), doi:http://dx.doi.org/10.2807/1560-7917.ES.2016.21.34.30326.
[9] Nielsen NM, Midgley SE, Nielsen AC, Christiansen CB, Fischer TK. Severe human parechovirus infections in infants and the role of older siblings. Am J Epidemiol 2016;183:664–70, doi:http://dx.doi.org/10.1093/aje/kwv206.
[10] Izumita R, Deuchi K, Aizawa Y, Habuka R, Watanabe K, Otsuka T, et al. Intrafamilial transmission of parechovirus a and enteroviruses in neonates and young infants. J Pediatric Infect Dis Soc 2018(1), doi:http://dx.doi.org/10.1093/jpids/piy079 [Epub ahead of print].
[11] Britton PN, Dale RC, Nissen MD, Crawford N, Elliott E, Macartney K, et al. Parechovirus encephalitis and neurodevelopmental outcomes. Pediatrics 2016;137:e20152848, doi:http://dx.doi.org/10.1542/peds.2015-2848.
[12] Britton PN, Khandaker G, Khatami A, Teutsch S, Francis S, McMullan BJ, et al. High prevalence of developmental concern amongst infants at 12 months following hospitalised parechovirus infection. J Paediatr Child Health 2018;54:289–95, doi:http://dx.doi.org/10.1111/jpc.13728.
[13] Bissel SJ, Auer RN, Chiang CH, Kofler J, Murdoch GH, Nix WA, et al. Human parechovirus 3 meningitis and fatal leukoencephalopathy. J Neuropathol Exp Neurol 2015;74:767–77, doi:http://dx.doi.org/10.1097/NEN.0000000000000215.