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Clinical utility of serum samples for human parechovirus type 3 infection in neonates and young infants: The 2014 epidemic in Japan

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Summary During the 2014 human parechovirus type 3 (HPeV3) epidemic in Niigata, Japan, this prospective observational study identified HPeV3 from 43/85 (51%) febrile young infants <4 months using PCR analysis of serum (n = 42) and/or cerebrospinal fluid (CSF) (n = 32) and genetic sequencing of the VP1 region of HPeV3. HPeV3-infected patients (median age, 32 days; range, 4–113 days) were diagnosed as having sepsis (79%), sepsis-like syndrome (19%), or encephalitis with septic shock (2%). Other than fever, mottled skin (67%) was significantly more frequent in HPeV3-infected patients than other virus-infected patients ($P = 0.005$). The rate of HPeV3 RNA detection in CSF without pleocytosis was high (88%; 28/32). Among the 32 patients whose serum and CSF samples were available, all patients were positive for serum PCR; however, 4 (12%) patients were negative for CSF PCR. Serum HPeV3 RNA level on admission was associated with younger age ($P = 0.002$), bad temper ($P = 0.041$), and grunting ($P = 0.008$). Among 6 patients with sequential data on serum HPeV3 RNA level, levels decreased rapidly without specific therapy. In conclusion, serum samples at disease onset are the most useful compared to CSF in detection of HPeV RNA and serum HPeV3 RNA level on admission was associated with important clinical manifestations in HPeV3-infected patients.

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Introduction

The human parechoviruses (HPeVs) are RNA viruses closely related to enteroviruses (EVs), in the family *Picornaviridae*.[1] Human parechovirus type 3 (HPeV3) causes sepsis and meningoencephalitis in neonates and young infants principally in children aged <3 months.[1,2] Because severe disease caused by HPeV3 infection can lead to neurologic sequelae[3,4] and death,[5,6] HPeV3 infection should be included in differential diagnoses of neonates and young infants who develop sepsis-like syndrome, sepsis, or meningoencephalitis.[5,7,8] However, polymerase chain reaction (PCR) for EVs does not detect HPeVs; thus, specific primer sets and probes are required for detection of HPeVs.[2]

After discovery of HPeV3 in 2004,[9] there have been an increasing number of reports of sepsis-like illness or sepsis,[5,10,11] meningitis,[7] and encephalitis[3] in children with HPeV3 infection. Clinical signs of HPeV3 infection in young infants include abdominal distention and umbilical protrusion,[12,13] and palmar–plantar erythema.[14] HPeV3 epidemics have been reported prospectively and retrospectively in many countries and regions, including Europe,[4–7,15–19] the United States,[20] Australia,[21] Middle East,[22] and Asian countries.[8,14,23–25] In Japan, epidemics of HPeV3 infection have occurred every 2–3 years since 2006.[24]

The definition of HPeV3 infection varies in previous reports—from detection of HPeV3 in any type of sample (e.g., stool and throat samples) to detection restricted to samples from sterile sites, such as blood and/or cerebrospinal fluid (CSF). Additionally, genotyping of clinical samples was not always performed in past studies. This inconsistency in the definition of infection and lack of genotype confirmation could have led to erroneous classification of patients infected by pathogens other than HPeV3.

An HPeV3 epidemic occurred in Niigata, Japan, in 2014, three years after the last epidemic in Japan. Although selected public health laboratories in Japan perform viral culture and PCR for HPeVs as part of active disease surveillance, the collected samples are usually stool or nasopharyngeal samples, which are not from sterile sites. In addition, the reporting sites are sporadic and not well organized. Since 2012, we have been monitoring viral pathogens—including HPeVs, EVs, herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)—that cause sepsis and meningoencephalitis in neonates and young infants. In June and July 2014, the epidemic was recognized by detecting HPeV3 RNA from serum and/or CSF from neonates and infants who presented with fever and tachycardia with mottled skin (Fig. 1). The objectives of this study were to investigate clinical manifestations of HPeV3 infection in patients with positive PCR results for serum and/or CSF and identify factors associated with these manifestations.

Materials and methods

Patients and samples

This prospective observational study evaluated viral etiology in febrile young infants (age, <4 months) at Niigata University Hospital and its 40 affiliated hospitals in Niigata Prefecture (approximate population <5 years of age, 88,000), Japan, during 2014. When neonates and young infants were suspected of having sepsis or meningoencephalitis, serum and/or CSF were collected within 2 days of disease onset, frozen, and sent to the laboratory at Niigata University for PCR testing. Real-time PCR for EVs,[26] HSV-1 and HSV-2,[27] and HPeVs[28] were routinely performed. HPeV3 infection was diagnosed if there was a positive result for HPeV RNA serum and/or CSF followed by genotyping based on sequence analyses of the VP1 region of the virus,[29] or if there was a fourfold or greater increase in neutralizing antibody titers to HPeV3.[30] The results of real-time PCR were sent back to physicians within 3 days after receiving

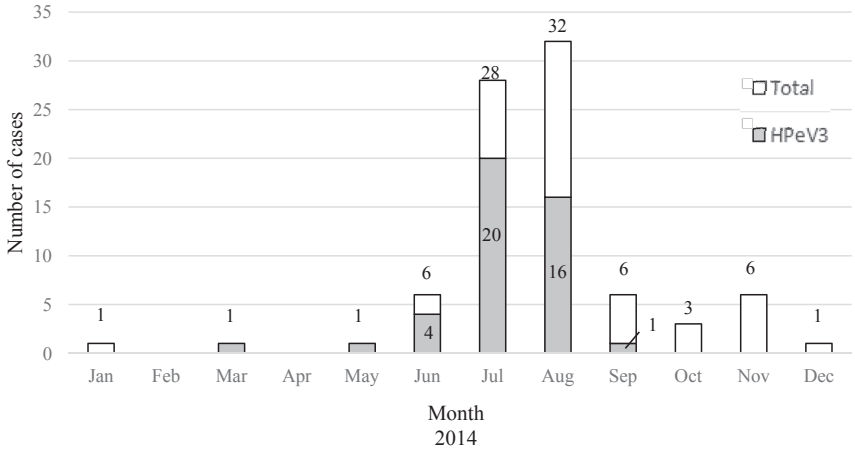

Figure 1 Numbers of neonates and infants (age, <4 months) who were admitted in 2014 to hospitals in Niigata, Japan, with a diagnosis of sepsis or sepsis-like illness and had a positive result for human parechovirus type 3 in a serum and/or cerebrospinal fluid sample, by month. Bars indicate the numbers of patients who were admitted to hospitals with a diagnosis of sepsis or sepsis-like syndrome and underwent evaluation of viral etiology after a febrile episode. The gray segments of the bars indicate the numbers of patients who were positive for human parechovirus type 3 in serum and/or cerebrospinal fluid. The numbers are cases for each month. The peak for HPeV3-infected cases was in July and August 2014.