The Molecular Diagnosis of Parechovirus Infection: Has the Time Come?

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(See the article by Sedmak et al, on pages 357–61.)

Human parechoviruses (HPeVs) as a distinct entity are largely unknown to clinicians and often forgotten by diagnostic virologists. In this issue of Clinical Infectious Diseases, Sedmak et al [1] report the association of HPeV with sudden unexplained infant deaths. Over a period of 17 years, the Milwaukee County Medical Examiner’s Office and the City of Milwaukee Health Department Laboratory investigated the role of viruses in deaths of children aged <2 years. Although enteroviruses and adenoviruses were the most commonly identified viruses, HPeV type 1 (HPeV1) was isolated from 18 decedents, HPeV type 3 (HPeV3) from 3, and HPeV type 6 (HPeV6) from 1. These are the first confirmed cases of HPeV3 and HPeV6 infection in the United States, as well as the first fatal cases associated with HPeV3.

In 1956, what we now call HPeV1 and HPeV type 2 were first isolated by Wigand and Sabin [2] from the stool samples of 2 children with diarrhea in Ohio, and the isolates were designated echovirus types 22 and 23, within the enterovirus genus of the Picornaviridae. Although HPeVs share many properties and disease manifestations with enteroviruses, differences were recognized from the beginning. When molecular methods were developed for the diagnosis of enterovirus infection in the 1990s, it became clear that echovirus types 22 and 23 were not detected using pan-enterovirus polymerase chain reaction (PCR) primers [3]. Thus, in 1999, HPeVs were designated as a separate genus of the Picornaviridae family [4]. Since then, the number of HPeV types has increased from 2 to 14, and many more are likely awaiting discovery (http://www.picornastudygroup.com/types/parechovirus/hpev.htm).

HPeVs are difficult to culture, and Vero cells, the optimal cell line, are not commonly used in clinical laboratories in the United States. Thus, HPeV infections have long been underdiagnosed. Ironically, as more sensitive methods have been developed to detect HPeV in research studies, diagnosis in clinical laboratories in the United States has decreased because of the change from conventional cell cultures to enterovirus molecular amplification tests. In short, diagnosis of HPeV infection has gone from bad to worse. Few clinical laboratories and perhaps only 1 commercial laboratory in the United States offer Parechovirus PCR. Typing of HPeV-positive isolates is confined to research laboratories. Therefore, it is not surprising that HPeV3 and HPeV6 infections have not previously been reported in the United States.

HPeV1 has been the most common HPeV identified to date. HPeV1 is primarily associated with asymptomatic or mild respiratory and gastrointestinal infection and less frequently with central nervous system disease. The majority of HPeV1 infections occur in children aged <1 year, and almost all children are infected by age 5. Severe disease is rare [5].

Of the newly recognized HPeV types, HPeV3 has garnered the most attention. HPeV3 was isolated from the stool sample of a 1-year-old in Japan with transient paralysis, fever, and diarrhea in 1999 but was first published in 2004 [6]. Shortly thereafter, enterovirus-like isolates from 3 infants in Canada with neonatal sepsis were identified as HPeV3 [7]. HPeV3 has subsequently been shown to be specifically associated with sepsis and fever in young infants, especially those aged <3 months [8, 9] and those with neonatal encephalitis with white matter injury [10]. HPeV3 is the most common HPeV recovered from cerebrospinal fluid (CSF) and appears to have a biannual cycle. Possible reasons for HPeV3 pathogenicity include use of different cell receptors accounting for its greater neurotropism, as well as a lower seroprevalence than HPeV1 in adults, resulting in a lack of protective maternal antibody in neonates [5, 9].

HPeV6 was originally isolated from the CSF of a 1-year-old with Reye syndrome but has since been recovered from stool and respiratory tract samples [11, 12]. Along with HPeV1 and HPeV3, HPeV6 is
1 of the 3 most commonly detected HPeV types worldwide [12].

In the current study, clinical information is provided only for the 4 infants from whom HPeV3 or HPeV6 were recovered. HPeV3 potentially contributed to the deaths of 2 infants who had upper respiratory symptoms in the days preceding death. Both were found unresponsive in their cribs in a prone position, which is now recognized as a significant contributing factor to sudden unexplained infant death. By history, concurrent infections in family members were likely. The third child with HPeV3 infection had chronic lung disease but no acute symptoms and died after she pulled out her tracheostomy tube. The infant with HPeV6 infection died of blunt trauma and had no symptoms attributable to HPeV infection.

All 4 children, even those without symptoms, had HPeV detected in multiple sites, including nasopharynx, stool, lung, and/or spleen. Because viremic dissemination is part of the normal pathogenesis of enterovirus and HPeV infections, little can be concluded from the detection of virus in multiple sites other than confirmation of acute infection.

Sedmak et al [1] state that theirs is the first report of an HPeV3 associated death. It should be noted that viral infection is generally thought to be a contributing risk factor rather than the cause of death in sudden unexplained infant death, and a mild respiratory virus or enterovirus infection is seen in up to 80% of infants with sudden unexplained infant death in the days preceding death [13]. Thus, the association of HPeV with sudden unexplained infant death is not unexpected. Indeed, given the insensitivity of culture, the number of HPeV infections has most certainly been underestimated.

Most importantly, this report, along with other recent publications [7–10, 14], calls our attention to the ubiquity and potential seriousness of HPeV infection in young children and the need for better diagnostic testing. The difficult question is at what point should tests move from the research to the clinical laboratory? As pathogen discovery methods improve and new viruses are recognized, this question will arise more frequently. In the absence of specific therapy, will a laboratory diagnosis change patient management and improve outcomes? Or will testing merely increase the cost of care? In hospitalized patients or fatal cases, is finding an answer reason enough? It is an unfortunate fact that cost-effectiveness data in different risk groups and settings are largely unavailable for virology tests.

One exception is molecular testing of CSF for enterovirus in hospitalized children, which has been shown to reduce antibiotic usage, unnecessary testing, and duration of hospital stays [14, 15]. Because HPeV causes clinical syndromes similar to enterovirus in very young persons, offering HPeV and enterovirus PCR as a diagnostic panel for hospitalized children aged <5 years with compatible clinical syndromes would be a logical starting point and should provide the greatest yield. Using this strategy, Wolthers et al [14] reported that HPeV molecular methods increased the viral detection rate by 31% in neonatal sepsis and meningitis in children aged <5 years.

HPeV PCR methods have been published, but there are no United States Food and Drug Administration–approved HPeV PCR kits. Thus, the task will fall to a limited number of academic centers, public health laboratories, and commercial laboratories capable of validating home-brew molecular tests for clinical use and of performing the test frequently enough to impact patient care. Much work remains for researchers to elucidate the role of various HPeV types in disease, but clinical laboratories can and should begin to assess the disease burden caused by HPeV in young, hospitalized children.

Acknowledgments


References