

The particulars on parechovirus

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Testing for human parechovirus (HPeV) is now available in many Canadian laboratories. The purpose of the present article is to aid clinicians in knowing when to order and how to interpret HPeV testing.

HISTORICAL BACKGROUND

HPeV are nonenveloped, positive-sense, single-stranded RNA picornoviruses that were first detected in 1956 in children with diarrhea. HPeV-1 and HPeV-2 were originally believed to belong to the genus *Enterovirus* (EV) and were named echoviruses 22 and 23 (1). In 1999, HPeV were assigned their genus name when genomic sequencing proved that they were not EV. At least 14 other HPeV types have been identified (Table 1) (2-34), starting with HPeV-3, which was initially reported in Japan in 2004 (21) and next reported in Canada in 2005 (35). Recombination between HPeV types may occur (31).

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

HPeV infection occurs worldwide. The spectrum of disease is far from fully elucidated. Transmission is believed to occur via the fecal-oral and respiratory routes (16). Reports of onset of symptoms in the first two days of life (36) and detection in cerebrospinal fluid (CSF) on day 2 of life (37) suggest that in utero transmission occurs. Severe disease associated with EV is common if the onset is in the first 10 days of life, presumably because the infant was exposed to a large dose of EV and no antibodies across the placenta; it is not yet clear whether this is true for HPeV. HPeV is not known to be teratogenic, but has been detected in three infants two to eight months of age with congenital anomalies (11).

Table 1 summarizes possible clinical manifestations of HPeV according to type. It is important to recognize that in some cases, there is only one case report. Even in the larger case series, there were no controls. There is convincing evidence that HPeV-3 causes neonatal sepsis and central nervous system (CNS) infection. As is the case for EV, most infections with HPeV are believed to be asymptomatic; therefore, all other clinical manifestations shown in Table 1 could be due to another agent during an asymptomatic infection with HPeV.

Seroprevalence to HPeV-1 falls after birth as maternal antibodies wane and then rise rapidly, with eight of nine children one to two years of age and almost all adults being seropositive in a study from Finland (38). Consistent with this, when routine monthly stool samples were collected, 43% of infants in Norway had documented infection by one year of age and 86% by two years of age, primarily with HPeV-1 (76%), with no association between infection and symptoms (2). This almost universal infection early in life does not appear to occur with HPeV-3, with a small study from Japan showing a seroprevalence of 15% at seven to 12 months of age, 45% at two to three years of age and 85% at four to six years of age (21). A study involving adults in Finland and the Netherlands showed seroprevalence rates of >85% for HPeV-1 and HPeV-2 and 35% to 75% for HPeV-4, -5 and -6, but only approximately 10% for HPeV-3 (39). None of 59 adults tested for HIV in Milwaukee (Wisconsin, USA) had antibodies to HPeV-3 (26). It has been postulated that most symptomatic HPeV-3 infection occurs in the first few months of life because a lack of maternal antibodies leaves infants vulnerable, suggesting that either antibody levels wane or that HPeV-3 is a relatively new type of HPeV (17). Antisera to HPeV-1 and HPeV-2 do

not neutralize HPeV-3 (40). Reinfection within a three-year period is common, but is almost always with a different type (2).

To examine the full spectrum of HPeV disease, samples submitted for EV testing 2009 through 2012 in Denmark were retrospectively tested for HPeV, with 149 of 4804 children (3%) having at least one positive sample (25 from CSF, 105 from stool, eight from pharynx/tonsil, two from bronchoalveolar lavage and nine from autopsy specimens) (1). HPeV was detected in more than one site in some children, although details were not provided. The types detected were HPeV-3 (n=90), HPeV-1 (n=21), HPeV-6 (n=8), HPeV-5 (n=4) and HPeV-4 (n=2), with all 25 positive CSF samples being HPeV-3. HPeV-3 was detected primarily in infants (mean age 1.6 months) while the mean age for HPeV-1 detection was 8.9 months. The positive autopsy specimens were from nine children of unspecified age with unexpected death; came from abdominal lymph nodes (n=5), bowel (n=3) and pulmonary tissue (n=1); and were HPeV-1 (n=4), HPeV-3 (n=2), HPeV-5 (n=1), HPeV-6 (n=1) and type not available (n=1). Seasonality was similar to EV, with most infections occurring in summer and fall.

In an attempt to determine how commonly diarrhea is attributable to HPeV, stools that were negative for rotavirus, norovirus, adenovirus, sapovirus and astrovirus were tested for HPeV in Japan and 20 of 247 (8%) were positive, with 15 of the 17 (88%) that were typed being HPeV-1 (41). A similar study from China (9) found that 21 of 328 (6%) stool samples were positive for HPeV alone while another 23 had another virus and HPeV, with the 44 types being HPeV-1 (n=32), HPeV-3 (n=4), HPeV-6 (n=4), HPeV-4 (n=2) and HPeV-14 (n=1). The mean age of patients with stools positive for HPeV was 15 months in the study from Japan and 11 months in the study from China, with all children being <5 years of age. There was no control group in either study; thus, the link between HPeV and diarrhea remains unclear.

A multicentre study from the Netherlands compared the clinical features of HPeV with EV. Of 258 children up to 16 years of age with suspected EV infections, 44 (15%) had HPeV and 140 (49%) had EV detected. The median age was 68 days for HPeV and 50 days for EV, with the children with HPeV having a lower incidence of meningitis (36% versus 54%; $P=0.046$), more gastrointestinal symptoms (30% versus 15%; $P=0.03$) and more hospital admissions (98% versus 86%; $P=0.026$) (42).

Similar to EV, a wide variety of rashes have been described with HPeV infection. A distinctive rash on the distal extremities involving the palms and soles of 12 of 15 neonates with HPeV-3 has been described in only one study to date (18).

Another similarity to EV is the spectrum of CNS diseases associated with HPeV: acute flaccid paralysis, aseptic meningitis and encephalitis (16). There are only scattered case reports of acute flaccid paralysis due to HPeV (3,21,43,44) but more may be identified as testing becomes more common. Case series often combine HPeV aseptic meningitis with encephalitis because they can be indistinguishable in infants. Both occur almost exclusively in children <5 years of age, with encephalitis not described beyond infancy (16). In a study comparing HPeV with EV CNS disease, HPeV was more commonly associated with upper respiratory tract symptoms (seven of 12 [58%] versus seven of 43 [16%]; $P=0.01$) and seizures (five of 12 [42%] versus six of 43 [14%]; $P=0.05$) (19). Detection of EV and Dengue virus (45) in CSF with no pleocytosis is well

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described. However, this phenomenon appears to be even more common with HPeV and was documented in nine of 10 children with HPeV encephalitis (20), and in 65 of 66 children (46) and six of eight children (19) with HPeV detected in CSF. One plausible but controversial explanation is that detection of HPeV in the CSF of children with no pleocytosis and no apparent CNS symptoms may be due to leakage of virus from blood rather than actual CNS infection (47). Combining three case series, rash occurred in 17% to 60% of children with CNS disease (16).

CNS disease is usually attributed to type 3 HPeV; however, in a study from France in which 120 CSF samples in children up to one year of age submitted for 'viral testing' were tested for HPeV, genotyping was successful on five of nine positives: HPeV-3 (n=3), HPeV-1 (n=1) and HPeV-4 (n=1) (27). Clinical data were limited and it was not clear whether the children with types other than HPeV-3 had CNS disease or simply positive CSF samples. In a study from China (37), 28 of 31 children with 'CNS symptoms' and HPeV in CSF had HPeV-1, with a considerably higher median patient age (14 months) than in other series of HPeV CNS disease.

The frequency and characteristics of HPeV outbreaks is not clear. The first possible outbreak of HPeV-1 described was in a New York neonatal intensive care unit (NICU) in 1964 to 1965, with 18 symptomatic infants (5). All but one had coryza and seven had pneumonia. Another possible NICU outbreak was described from Israel in 1992 to 1993, with 19 cases including seven with possible necrotizing enteritis (12). There were seven infants with positive stools for HPeV-1 in July 2009 in a Croatia NICU (36). Three of the isolates were identical, with the others having up to three minor nucleotide differences. Six infants exhibited respiratory or gastrointestinal symptoms and the seventh was an asymptomatic contact. A possible outbreak was described in Japan in 2008, in which 40 of 876 patients of all ages had HPeV-3 detected from throat swabs (n=29), stool (n=24) and/or 'liquor' (presumably cerebrospinal fluid; n=5). No data are presented to confirm that this was in increased incidence over baseline (48).

HPeV disease may not be limited to the pediatric population. Outbreaks of myalgia were linked to HPeV-3 in 14 adults in 2008 and five adults in 2011 in Yamagata, Japan (24). HPeV (type not specified) was detected by polymerase chain reaction in four of 139 samples of intraocular fluid in adults with uveitis in the Netherlands (15). HPeV-1 was detected in the endotracheal secretions of a 78-year-old woman in Canada (49).

As expected for a virus that primarily causes infection in the first two years of life, there was no convincing evidence of a link between HPeV and the onset of type 1 diabetes in a study from Finland, although diabetic boys had more HPeV infections in the six months before the development of autoantibodies than did control boys (50).

PROGNOSIS

Most neonates with HPeV-3 sepsis survive, but the long-term outcomes are unknown. Aseptic meningitis with EV has never been clearly linked to death or sequelae, and the same is probably true with HPeV. In a case series of HPeV-3 encephalitis where nine of 10 children presented with seizures, follow-up showed five to have normal development, one to be too young to test and one each to have cerebral palsy, seizures, learning disabilities and hypertonias (20). Nine of the 10 children had periventricular changes in white matter on magnetic resonance imaging that extended into the subcortical region and evolved to gliosis (20). In other case series involving imaging with CNS disease, no abnormalities were found on head imaging in six children (45) or in 11 children (19) but not all had magnetic resonance imaging and perhaps some or all had aseptic meningitis rather than encephalitis.

LABORATORY DIAGNOSIS

Parechovirus has been detected in serum, plasma, throat swabs, nasopharyngeal swabs, bronchoalveolar lavage, stool, CSF and tissue biopsies, usually by molecular methods because most HPeV grow poorly or not at all in cell culture. When isolated in cell culture, the cytopathic effect of HPeV is similar to that of EV. Antibody neutralization was used to distinguish HPeV from EV in the past; however, laboratories now use

TABLE 1
Clinical manifestations of human parechovirus (HPeV) according to type

HPeV type	Clinical features*
1	Asymptomatic infection (2); acute flaccid paralysis (3), meningitis and encephalitis (4); coryza and pneumonia (5); acute otitis media (6); myocarditis (7); severe dilated cardiomyopathy (8); diarrhea (9,10) including bloody diarrhea (11); necrotizing enterocolitis (12); hemolytic uremic syndrome (13); lymphadenopathy (14); Reye's syndrome (11); uveitis [†] (15)
2	Mild gastrointestinal symptoms (1); mild respiratory symptoms (1); uveitis [†] (15)
3	Infant sepsis (16,17); infant meningitis (18,19), encephalitis (20), and transient paralysis (21); diarrhea (9,10); palmer-planter erythematous rash and maculopapular rash (18); neonatal hemorrhage-hepatitis syndrome (22); hemophagocytic lymphohistiocytosis-like syndrome (23); myalgia [†] (24); uveitis (15); sudden infant death syndrome (25,26)
4	Infant central nervous system disease (27); lymphadenitis (9,28); infant fever (28) and sepsis (29); gastroenteritis (10)
5	Diarrhea (9,10); acute flaccid paralysis (28)
6	Diarrhea (9); acute flaccid paralysis (3); Reye's syndrome (30);
7	Acute flaccid paralysis (3)
8	Gastroenteritis (31)
9	Unpublished
10	Gastroenteritis (10,32,33)
11	Diarrhea (10)
12	Diarrhea with acute flaccid paralysis (34)
13	Gastroenteritis (32)
14	Diarrhea (9); fever (32)
15	Diarrhea (32)
16	Unpublished

*These clinical features have been described in at least one patient shedding HPeV but there may be no relationship between HPeV and these signs or symptoms; [†]These clinical features have only been described in adults to date

molecular assays such as reverse transcriptase polymerase chain reaction, which are more sensitive than culture (42) and enable type assignment. In a study, children up to 16 years of age with suspected EV or HPeV routinely had multiple specimens submitted for RT-PCR for HPeV (with CSF submitted only if clinically indicated). Children were considered to be infected if HPeV was detected at any site. The sensitivity was 95% for stool, 85% for CSF, 79% for blood, 94% for a nasopharyngeal specimen and 57% for urine (42). Shedding in stool in healthy young children is estimated to persist for a median of 51 days (2).

TREATMENT

Although compounds are being tested for activity against HPeV-3 (17), there are no published data on efficacy for any licensed or experimental therapy. The search for antivirals for EV is at an impasse; thus, there is minimal hope that we will have such therapy for HPeV in the near future. Intravenous immunoglobulin is commonly used as an unproven therapy for severe EV; however, given the low HPeV-3 seroprevalence in adults, one would postulate that it is unlikely to be effective for HPeV-3 infection.

CONCLUSION

Parechovirus is an evolving pathogen that primarily causes sepsis and CNS disease in neonates, with all other clinical manifestations remaining unproven. Laboratory diagnosis of HPeV is still an evolving field. Detection of HPeV in the CSF of a newborn with encephalitis should be considered diagnostic, whereas detection in the stool or nasopharynx of an older child may reflect coinfection, with all symptoms attributable to another agent.

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