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Parechoviruses in children: understanding a new infection

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Purpose of review

Human parechoviruses (HPeVs) within the large and growing family of *Picornaviridae* are common human pathogens associated with a wide spectrum of disease presentations. Although 10 different HPeV types have been published to date, there is increasing evidence for a specific role of HPeV type 3 (HPeV3) in severe neonatal disease. In this review, we will describe both the disease associations and underlying epidemiological and/or biological basis for the often marked differences in disease outcomes between HPeV types.

Recent findings

Application of molecular-based diagnostic techniques has revealed an association between neonatal sepsis, encephalitis and hepatitis with HPeV3 but not with other parechovirus types. HPeV3 shows evidence for very recent emergence in human populations as well as inferred differences in cellular receptor usage.

Summary

The recently discovered HPeV3 has been shown to play an important role in severe neonatal infections, observations possibly linked to its very recent emergence or possibly different cellular tropism that underlie its targeting of the most susceptible individuals. HPeV infections are currently under-diagnosed and should be considered in the clinical and diagnostic evaluation of severe neonatal disease presentations.

Keywords

encephalitis, neonatal infections, parechovirus, picornavirus, sepsis

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Introduction

Human parechoviruses (HPeVs) are small, nonenveloped, single-stranded and positive-sense RNA viruses within the Parechovirus genus of the large *Picornaviridae* family (Fig. 1). The HPeV genome is approximately 7400 bases in length, and encodes a single polyprotein flanked by 5′ and 3′ untranslated regions (UTRs). The polyprotein is post-translationally cleaved into three structural viral proteins (VP1–VP3) and seven nonstructural proteins (2A–2C and 3A–3D) (Fig. 2).

The first two HPeV types, originally described as echoviruses 22 and 23 within the Enterovirus genus, were isolated over 50 years ago, whereas a further eight HPeV types known to infect human have been only very recently identified. Infections are enteric and often associated with mild gastrointestinal and respiratory symptoms, although severe neonatal diseases including sepsis, meningitis, encephalitis and hepatitis have been described. Intriguingly, these more severe disease outcomes have been specifically linked to infection with a newly emergent HPeV type 3 (HPeV3). The recent evidence for its greater pathogenicity in neonates and the underlying differences in epidemiology and host interactions will be the primary focus of this review.

Human parechovirus infections

Human parechovirus infections are extremely widespread worldwide but historically infrequently recognized or diagnosed as a cause of human disease. Part of the reason for this is the often inapparent or misunderstood nature of their infections that typically target children under the age of 2 years, and difficulties with their detection by traditional virus diagnostic techniques such as virus isolation [3]. Indeed our current greater understanding of the frequency and disease associations of HPeVs has been gained through the recent development of molecular detection methods. The widely used reverse-transcriptase polymerase chain reaction (RT-PCR) assay is much faster and has far greater sensitivity and specificity, particularly for those HPeV variants associated with more severe disease [4,5•,6–10]. However, routinely used enterovirus RT-PCR will fail to detect HPeVs due to genetic differences between these viruses and thus HPeV-specific RT-PCR has to be used. Primers targeting the highly conserved 5′UTR allow

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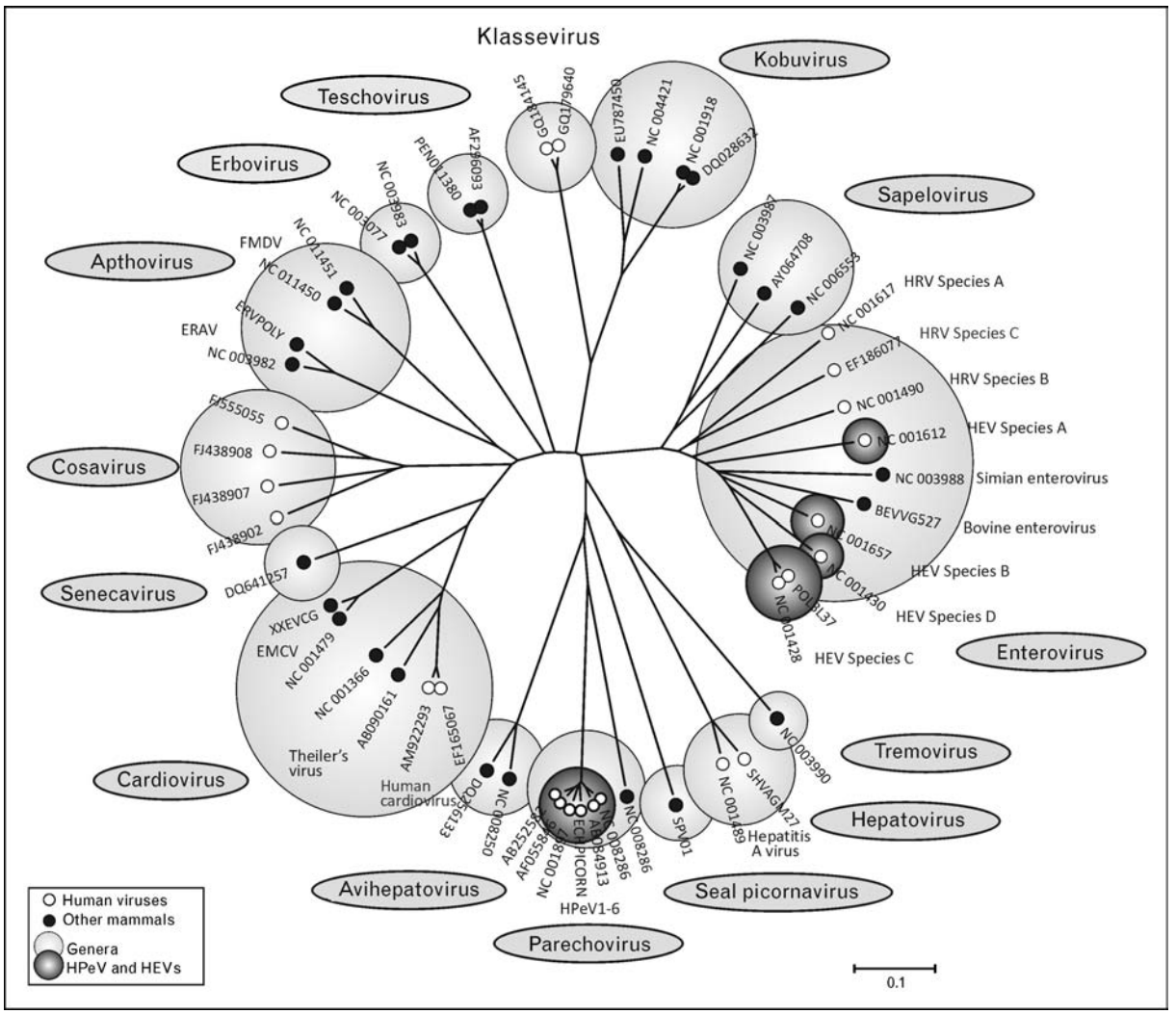
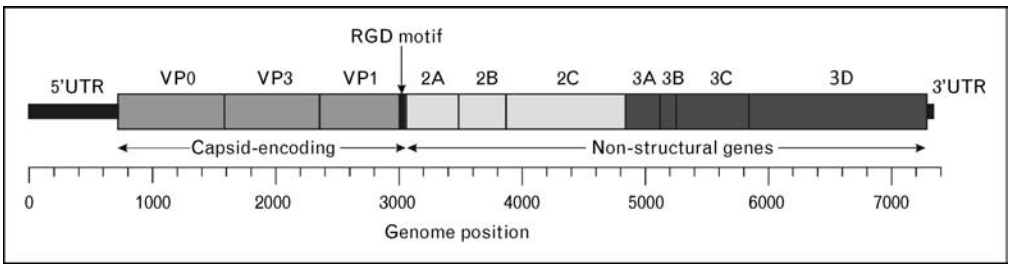
Figure 1 Evolutionary relationship of human parechovirus to other picornaviruses: classification into genera and species



Evolutionary tree of picornaviruses showing its division into 14 designated or proposed genera (enclosed within bubbles), and the human enterovirus and parechovirus groups highlighted in dark gray. The tree was constructed by comparisons of amino acid sequences of the 3Dpol region [positions 5711–7252 in the prototype Harris genome (accession number L02971)]. EMCV, encephalomyocarditis virus; ERAV, equine rhinitis virus; FMDV, foot and mouth disease virus; HEV, human enterovirus; HPeV, human parechovirus; HRV: human rhinovirus. The status of the recently described group of human enteric viruses labelled Klassevirus [1] is undecided and may be eventually included within the *Kobuvirus* genus.

Figure 2 Genome organization of human parechovirus



Genome organization of parechoviruses coding for a single polyprotein. This is cleaved to form structural (gray) and nonstructural proteins (light gray and black) for replication and virus particle formation. The RGD motif used for integrin binding and entry in HPeV1, 2, 4–6 is arrowed. Information on the demonstrated or inferred functions of the individual virally encoded proteins are summarized in [2].

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equally sensitive detection of all known HPeV types, whereas the amplification and sequencing of the highly variable VP1 region enables reliable type identification of HPeV-positive samples [9,11••,12].

Human parechovirus types

The use of RT-PCR and molecular virus discovery methods has dramatically increased our knowledge of the prevalence, genetic diversity and range of clinical presentations associated with different HPeV types. HPeV types 1 and 2 (previously known as echovirus 22 and 23, respectively) were discovered in USA from children with diarrhoea in 1956 [13]. HPeV3 was identified in Japan from a 1-year-old child with transient paralysis, fever and diarrhoea in 1999 [14] and almost simultaneously was also recovered from nasopharyngeal aspirates of neonates with suspected sepsis in Canada [15]. Another new HPeV type, HPeV4, was isolated from a stool sample of a neonate with febrile illness in the Netherlands in 2002 [16], but has been since shown to have circulated at least from the 1970s [17,18]. HPeV5 was first identified in USA in 1986 from a 2-year-old child with high fever [19], but this virus was originally assigned as HPeV2 based on incorrect neutralization data and has only recently been classified as a fifth type based on genetic analysis [18]. HPeV6 was isolated from a cerebrospinal fluid (CSF) specimen of a 1-year-old child with Reye's syndrome in Japan [20]. Very recently HPeV7 was identified from the stool sample of a healthy Pakistani child who had been in contact with a case of acute flaccid paralysis (AFP) [21], whereas screening a faecal sample collection from Brazilian children with acute diarrhoea revealed another novel HPeV type, HPeV8 [22]. The remaining HPeV types shown to infect human (10 and 14) have been identified only very recently from the Netherlands, Sri Lanka and Thailand [12,23,24]. The host origin (human or primate) of the other unpublished HPeV variants (types 9, 11–13) listed on http://www.picornastudygroup.com/types/parechovirus/hpev.htm is uncertain.

Epidemiology of human parechovirus infections

Despite the original detection of several of these virus types in association with diarrhoea, neonatal febrile illness and central nervous system (CNS) diseases, HPeV primarily causes clinically inapparent or unrecognized infections in young children. Through detection of antibodies to HPeV, it has been shown that over 90% of children have been infected with at least one HPeV type by the age of 2 years [6,25]. Targeting of this age group is also apparent by observations over 30 years ago that 60% of 580 HPeV isolates originated from children under the age of 1 year [26]. Similarly, surveillance data in the USA between 1983 and 2005 revealed 73% of 456 HPeV1 infections and 68% of 34 HPeV2 infections occurred under the age of 1 year [27], whereas in the Netherlands from 2000 onwards almost all HPeV1 and HPeV3 infections have been recorded in children under the age of 3 years [28,29••]. Evidence for its high incidence in this group was provided by a recent longitudinal community-based study of Norwegian children under the age of 2, where 11.3% of 1941 faecal samples were HPeV-positive irrespective of presenting symptoms [30]. Remarkably, there are only four studies in the current literature of HPeV infections in individuals over the age of 10 years [20,31–33]. Studies of disease complication of HPeV must therefore take into account the high background incidence and overwhelmingly clinically inapparent nature of HPeV infections in young children.

Neonatal infections

The primary site of HPeV replication is thought to be the respiratory and gastrointestinal tract; replication in the intestine leads to prolonged shedding of infectious virus in faeces readily detectable by virus isolation and RT-PCR methods. In addition to faecal/oral transmission, infections may also occur through respiratory routes, with infection and virus shedding detectable in respiratory secretions. Furthermore, virus can spread via the blood stream to other organs causing systemic illness. HPeV type 3 has been recently shown to be an important cause of severe infections in very young children including sepsis, encephalitis and hepatitis. These clinical manifestations overlap with those produced by enteroviruses, and disease is often indistinguishable without specific virological diagnosis.

To clinically exclude sepsis in newborns less than 90 days old with fever (defined as a temperature >38°C) is problematic, and a term 'neonatal viral sepsis' has been widely used to describe pyrexia in neonates with a high fever without an identifiable bacterial cause. Wolthers *et al.* [29••] have defined sepsis-like viral illness as fever or hypothermia with signs of circulatory and/or respiratory dysfunction measured by tachycardia or bradycardia, low blood pressure and decreased oxygen saturation. However, study participants described as having sepsis clinically but without fulfilling the above criteria [29••] and those without sufficient data provided to define sepsis-like viral illness [11••,15], are referred to as suspected sepsis in the remainder of the review. Furthermore, neonatal sepsis can range in severity from a nonspecific febrile illness to potentially fatal multisystem disease often with respiratory or gastrointestinal symptoms, CNS involvement manifesting as meningitis, encephalitis or meningoencephalitis, or have evidence of hepatitis. Causative studies of neonatal sepsis during the first month of life yielded a bacterial cause in approximately 10–15% of patients, with the remaining febrile neonates assumed to have a viral infection most commonly caused by enterovirus [34]. However, the potential role of HPeV as a cause of severe neonatal

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infection has only much more recently been systematically investigated.

Several studies describe HPeV detection in association with neonatal sepsis in studies from Canada, the Netherlands, UK and USA [11••,15,28,31,33] and have also been linked with meningitis in young children [35]. In a Dutch study, HPeV was detected by real-time RT-PCR in 4.2% of 761 CSF samples from children under the age of 5 years [28,29••]. Most of these children presented with defined or suspected sepsis-like illness (15/29 and 6/29, respectively), whereas meningitis (3/29) or encephalitis (1/29) were also seen. The median age of these HPeV-positive children was 1.2 months. In a recent study from Scotland, 14 from 1575 CSF samples were HPeV-positive on screening by RT-PCR, each of which originated from infants less than 3 months of age with suspected sepsis or pyrexia. HPeV typing of these CSF samples revealed all infection to be due to HPeV3, despite the circulation of predominantly HPeV1 in the local community [11••]. The incidence of severe HPeV3 infection (and of suspected neonatal sepsis) followed the same biannual cycle as noted previously from faecal samples [11••,12,28,35], with the highest frequency in 2008 (7.2%) exceeding that of enteroviruses [11••]. The association of HPeV3 with neonatal sepsis is consistent with previous studies from smaller sample numbers implicating this specific parechovirus type [10,36••], and with the rarity of other types [1,2,4,5•] in sepsis cases [3,16–18,28,31].

Neonates with HPeV encephalitis present similarly to enterovirus infection, the most frequent signs being fever, seizures, irritability, rash and feeding problems [37••]. A recent study described 10 newborn infants with HPeV3 confirmed encephalitis, who all except one presented clinically with seizures and had periventricular white matter changes confirmed by magnetic resonance imaging [36••]. Furthermore, pleocytosis was found in only 1 of 10 patients studied, and the protein and glucose levels remained normal in all cases [37••]. Normal CSF findings can therefore be misleading when diagnosing neonatal HPeV infection. The neurodevelopmental outcome was variable with cerebral palsy in one, learning disability at 7 years of age in one, epilepsy in one, suspected developmental abnormalities at 18 months in one and normal neurodevelopment in six children [36••]. Interestingly, data from animal experiments suggest that enterovirus infections acquired in the neonatal period may persist in the CNS as a low-level, noncytolytic infection, causing ongoing inflammatory lesions [38]. It might therefore be speculated that these longer effects of HPeV infection in neonates may similarly reflect ongoing damage to the CNS arising from persistence.

HPeV3 was recently identified as a cause of neonatal hepatitis-coagulopathy syndrome [39•]. This neonate presented with high fever, and was found to have abnormal liver enzymes 4 days later (AST 5421 U/l and ALT 1207 U/l). He also developed significant coagulopathy and thrombocytopenia on hospital day 7, but within 9 days from admission his hepatitis, coagulopathy and thrombocytopenia resolved. Hepatitis with coagulopathy caused by HPeV3 has also been described in Scottish neonatal twins [33]. As an emerging pathogen, HPeV3 (and other types) appears to display a wide variety of clinical presentations including neonatal sepsis, meningitis, encephalitis and hepatitis, and is probably more common than previously suspected.

Infections with other parechovirus types

HPeV types 1, 2, 4 and 6 have been associated with gastroenteritis in several different studies [40,41], but their role as a cause of enteric disease is to be definitely established. Detection in at least some cases most likely represents asymptomatic carriage and is incidental to gastroenteritis from another cause. Although HPeV1 has been linked clearly with acute otitis media [42], the association between HPeV types 1, 3, 4, 5 and 6 and respiratory tract disease is less well defined [9,31,40] and requires further studies to establish a causal relationship. In addition to HPeV3, HPeV1 has been linked with sporadic cases of aseptic meningitis [26], encephalitis [41], encephalomyelitis [43] and flaccid paralysis [32], whereas one of the HPeV2 strains was originally isolated from a child with aseptic meningitis [43]. A number of case reports and small studies propose associations of HPeV with a wide range of other diseases, including lymphadenitis (HPeV4; [20]), myositis (HPeV3; [17]), haemolytic uraemic syndrome (HPeV1; [44]), myocarditis (HPeV1; [45,46]), TORCH syndrome (HPeV4; [17]) and necrotizing enterocolitis (HPeV1; [47]). In addition, case reports describe HPeV1, HPeV3 and HPeV6 detection in sporadic cases of AFP in children [14,20,32]. Reye's syndrome, which is characterized as an acute, non-inflammatory encephalopathy with hepatic dysfunction and fatty infiltration, has been similarly associated with lethal HPeV5 [18] and HPeV6 infections [20]. Further studies, with improved diagnostic assays, are required to determine the frequencies of these disease associations relative to other viral and non-viral causes.

Treatment

The treatment of (neonatal) parechovirus infections is primarily supportive in the absence of specific antiviral therapy. The outcome of neonatal enterovirus infections has been shown to benefit from immunoglobulin therapy [48], although there are no data available to date to support its use in HPeV infections. Pleconaril is the most advanced antiviral treatment option for enteroviruses targeting the attachment, entry and uncoating of enteroviruses, although only limited data on its efficacy for

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neonatal enterovirus disease has been presented [49,50]. In recent in-vitro studies, pleoconaril has been shown to have no antiviral activity against HPeV (KW; unpublished data) and new treatment strategies are likely to be needed in future.

Epidemiological and biological basis for differences in pathogenicity

It is not known why HPeV3 is specifically associated with severe neonatal infections, but the underlying basis may be at least partly epidemiological. Infection and severe systemic disease in neonates that follows may occur more frequently in HPeV3 because frequencies of past infection with HPeV3 in adults may be lower than those of other HPeV types. As a consequence, neonates and young infants would not be protected as frequently by maternal antibody after birth as they would be from HPeV1 and possibly other types. This hypothesis is supported by the much lower observed seroprevalence of HPeV3 among women of child-bearing age in Japan (68% [14]) compared to close to universal adult seropositivity for HPeV1 [6,25]. The median age of the children infected with HPeV1 (6.6 months) was found to be significantly higher than HPeV3 (1.3 months) [28], a finding consistent with protection from HPeV1 by maternal antibody in the first half year of life. Indeed, more recent data document HPeV3 infections to occur almost exclusively in children under the age of 3 months [11••].

The lower adult seroprevalence of HPeV3 may be a direct consequence of its more recent emergence than HPeV and other types. Evidence for this is provided by observations of extremely restricted within-type sequence diversity of HPeV3 compared to other types. Our recent measurement of evolutionary rates in the VP3/VP1 regions of HPeV3 (2.83×10^{-3} substitutions per site per year meaning 1 in 400 nucleotide changes annually; over two-fold lower than for HPeV1) predicted a common ancestor for all currently circulating variants of HPeV3 in 1987 (range 1980–1992) [23], approximately 10 years before HPeV3 was first isolated (A308/99) in Japan and in Canada [14,15]. Although comprehensive worldwide genetic characterization of HPeV3 has yet to be performed, these findings are nevertheless consistent with the hypothesis for its relatively recent global spread into a previously unexposed human population. Its emergence may thus account for reduced adult exposure and maternal antibody protection, and therefore its specific targeting of neonates with immature immune systems and lack of maternal antibody protection. Substantiation of this hypothesis requires, however, much better data on the actual frequencies of HPeV3 exposure and immunity in countries where specific associations of this type with neonatal disease have been demonstrated. It further requires to be demonstrated that neonatal disease occurs specifically in children of mothers seronegative for HPeV3 at the time of birth, data missing from studies of this phenomenon published to date. A recent case report from Glasgow, UK [33] did, however, show that infection of twins in the neonatal period with HPeV3 (presenting with pyrexia, rash and hepatitis) occurred simultaneously with infection in the mother, consistent with the hypothesis for a lack of maternal HPeV3 exposure underlying these severe disease outcomes.

A biological explanation, that HPeV types differ intrinsically in their tissue tropism and ability to spread systemically, is additionally possible. The ability of picornaviruses to infect different cell types is primarily determined by expression of membrane proteins that serve as receptors for the virus. Many groups of picornaviruses, such as enteroviruses and aphthoviruses (a group containing foot-and-mouth disease virus; FMDV) show remarkable variability in their receptor interactions, a feature that likely extends to HPeV. In HPeV type 1, the C-terminus of the VP1 capsid protein contains an arginine-glycine-aspartic acid (RGD) motif [51,52] that is utilized by several viruses to enable virus attachment through binding to cell surface-expressed integrins. Among picornaviruses, these include FMDV and the enteroviruses coxsackievirus A9 (CAV9) and a Barty strain of echovirus 9. HPeV1 utilizes principally $\alpha_V\beta_1$, $\alpha_V\beta_3$, and $\alpha_V\beta_6$ integrins as its receptors [53–55]. Importantly, HPeV3 differs from most strains of HPeV1 and other HPeV types by not encoding an RGD motif in VP1 [14], implying use of a different cellular receptor for entry, although what this might be has yet to be determined.

The use of an alternative receptor may change the cellular tropism of HPeV3, and conceivably lead to an enhanced ability to spread and replicate in the CNS if the putative receptor was expressed in neural tissue and the integrins utilized by HPeV1 were not. On the basis of this hypothesis, biological differences from HPeV1 might also be expected in the more recently discovered HPeV types [7–10,11••,12–14] and a small subset of recently characterized variants of HPeV1 and HPeV5 variants that also lack RGD sequences in VP1 [12]. Future detailed clinical investigation of infection outcomes with these viruses will be required to evaluate the role of receptor use variability in HPeV pathogenesis.

Conclusion

The recent application of molecular methods for screening and type identification of HPeV has revealed greater prevalence, genetic diversity and heterogeneity in its epidemiology and clinical outcomes of infection than had been previously revealed by cell culture-based diagnostic methods. The recently discovered HPeV3 has since been shown to play an important role in severe

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neonatal infections, including sepsis, encephalitis and hepatitis. The pathogenic nature of this HPeV type is perhaps connected to its very recent emergence or distinct cellular tropism and virological properties that underlie its targeting of a distinct group of susceptible individuals. HPeV infections are currently under-diagnosed and should be considered, along with enteroviruses, in the clinical and diagnostic evaluation of severe neonatal disease presentations.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 278).

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This study presents clinical details of neonatal encephalitis and hepatitis-coagulopathy syndrome caused by HPeV3, which is important for further understanding HPeV disease.

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