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Review

Pediatric parechovirus infections

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ABSTRACT

Human parechoviruses (HPeVs) are members of the large and growing family of *Picornaviridae*. Although 16 types have been described on the basis of the phylogenetic analyses of the VP1 encoding region, the majority of published reports relate to the HPeV types 1–8. In pediatrics, HPeV1, HPeV2 and HPeV4–8 mainly cause mild gastrointestinal or respiratory illness; only occasionally more serious diseases have been reported, including myocarditis, encephalitis, pneumonia, meningitis, flaccid paralysis, Reye syndrome and fatal neonatal infection. In contrast, HPeV3 causes severe illness in young infants, including sepsis and conditions involving the central nervous system. Currently, the most sensitive method for detecting HPeV is real-time polymerase chain reaction assays on stools, respiratory swabs, blood and cerebrospinal fluid. However, although it is known that HPeVs play a significant role in various severe pediatric infectious diseases, diagnostic assays are not routinely available in clinical practice and the involvement of HPeV is therefore substantially underestimated. Despite long-term efforts, the development of antiviral therapy against HPeVs is limited; no antiviral medication is available and the use of monoclonal antibodies is still being evaluated. More research is therefore needed to clarify the specific characteristics of this relevant group of viruses and to develop appropriate treatment strategies.

Contents

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1. Introduction

Human parechoviruses (HPeVs) belong to the family of *Picornaviridae*, a highly diverse group of small, non-enveloped, single-stranded RNA viruses of positive polarity, many of which cause disease in humans [1]. The genera within the family include important pathogens such as rhinoviruses, enteroviruses, polioviruses and hepatoviruses. In comparison with other picornaviruses, HPeVs have a number of atypical biological and molecular properties, such as unusual cytopathic effects and the lack of cleavage of the VP0 protein into VP4 and VP2 (this last unusual characteristic has been reported also for Kobuvirus), which leads to a virion particle with only three rather than four capsid proteins [2]. Although 16 types have been described on the basis of the phylogenetic analyses of the VP1 encoding region, the majority of published reports relate to HPeV types 1–8. Type 1 (HPeV1) and type 2 (HPeV2) were discovered in children with diarrhea in the United States in 1956, initially designated as echovirus types 22 and 23. They were renamed in the early 1990s when the genus *Parechovirus*, which includes the two species of *Ljungan virus* and *parechovirus*, was defined [2]. In pediatrics, HPeV1 and HPeV2 cause mild gastrointestinal or respiratory illness; more serious diseases have been occasionally reported, including myocarditis, encephalitis, pneumonia, meningitis, flaccid paralysis, Reye syndrome and fatal neonatal infection [2,3]. HPeV3 not only causes mild gastrointestinal and respiratory tract illness, but also severe illnesses such as sepsis and conditions involving the central nervous system (CNS) [1,4], whereas HPeV4–8 seem to cause diseases similar to those associated with HPeV1 and HPeV2 infections [5].

The aim of this review is to summarize the available information concerning the epidemiology, clinical presentation, diagnosis and management of HPeV infections in the first years of life and to highlight priorities for future research.

2. Epidemiology of pediatric HPeV infections

HPeVs are common throughout the world. Like the other members of the *Picornaviridae* family, they replicate mainly in the gut and are transmitted by the fecal–oral route, although infections may also occur through respiratory routes and virus shedding is readily detectable in respiratory secretions [1]. This suggests that HPeVs can replicate also in the respiratory tract. The most predominant serotypes in childhood and adulthood are HPeV1, followed by HPeV3, HPeV4 and HPeV6 [1].

There are no published data concerning the seroprevalence of the other HPeVs types, but HPeV1 and HPeV3 infections in the first years of life have been studied in detail [1]. All children aged ≤1 year have antibodies against HPeV1, and so its seroconversion during the early months of life has been clearly established [2]. However, although the HPeV3/HPeV1 comparative proportions can be due to sampling biases, it has been reported that HPeV3 infects younger children more often than HPeV1 and is most frequent among infants below the age of 3 months [6,7], probably because of the immaturity of their immune system. HPeV3 infections are uncommon in subjects aged above the age of 10 years, although an unusual outbreak of epidemic myalgia in adults in Japan during June–August 2008 in Japan was associated with HPeV3 infection [8]. From a study conducted over a 5-year surveillance period, Harvala et al. have suggested that the lower adult seroprevalence of HPeV3 may be directly due to the fact that emergence is relatively more recent than that of HPeV1 and so it may not have spread sufficiently in the adult human populations [9]. This proposed scenario is different from that of HPeV1 as virtually universal seropositivity may account for the almost complete absence of HPeV1 disease in the first months of life [9].

HPeV1 infections have a seasonal pattern that is similar to that of human enteroviruses insofar as they typically occur more frequently in the late summer and early winter [10,11]. HPeV3 is once again different as it is characterized by bi-annual cycles of infections in Europe, which have occurred almost exclusively since 1988 [10,11].

Table 1 summarizes the main epidemiological studies of pediatric HPeV infections [9,11–17].

3. Pathogenesis

The majority of the pathogenetic studies also relate to HPeV1 and HPeV3 and suggest that the different clinical manifestations of the various types of HPeV may be explained by differences in their biological characteristics. It seems that HPeV3 lacks the arginine-glycine-glutamic acid sequence motif at the carboxyl terminus of VP1 that is characteristic for other HPeVs and is thought to mediate the use of integrins as cell receptors, thus suggesting that it may use a different receptor to enter cells with a potentially different tropism [10]. This unique receptor may explain why HPeV3 is associated with neonatal sepsis and CNS infection. In order to verify whether the *in vitro* replication kinetics of HPeV1 and HPeV3 are related to their pathogenicity, Westerhuis et al. used real-time polymerase chain reaction (PCR) to study isolated HPeV1 and HPeV3 strains in cultures of gastrointestinal, respiratory and neuronal cell lines [18]. They found no relationship between the clinical symptoms and *in vitro* replication of the HPeV1 strains, but the HPeV3 strains replicated more rapidly in neuronal cells, suggesting that there is a relationship with neuropathogenicity. They also found that HPeV1 could be efficiently neutralized by its specific antibody and intravenous immunoglobulins, whereas most HPeV3 strains could not be neutralized, which may explain the milder clinical course of HPeV1 infections. Triantafilou et al. made the interesting observation that toll-like receptors (TLR) 8 and TLR 7 seem to act as host sensors for HPeV1 [19]. TLR 8 and 7 are localized in endosomes where they sense viral genomic RNA which subsequently leads to the secretion of inflammatory and regulatory cytokines aimed at controlling the infection; this involvement of TLRs was not observed in the case of HPeV3 infections [19].

4. Clinical presentations of pediatric HPeV infections

HPeV infections in the first years of life can be associated with a wide variety of clinical presentations, ranging from asymptomatic infections or mild disease to severe disease symptoms, including sepsis, meningitis and encephalitis, which mainly occur in neonates and infants under the age of 3 months.

4.1. Sepsis-like illness and CNS infections

A number of cases of severe infections such as sepsis-like illness and CNS infections (meningitis or encephalitis) have been described in infants below the age of 3 months [20–23]. In a prospective study, Verboon-Maciolek et al. compared the clinical signs, diagnosis, laboratory data, cerebral imaging findings and neurodevelopment outcome of neonates and infants with HPeV infections with those children with enterovirus infections [21]. It was not possible to differentiate HPeV and enterovirus infections on the basis of their clinical presentations, but it was observed that HPeV mainly caused meningoencephalitis with no pleocytosis in cerebrospinal fluid and a significantly high protein level [21]. These findings have been confirmed by Sharp et al., who also found a low peripheral blood cell count with low absolute lymphocyte counts, high maximum temperatures, and a long duration of fever and hospitalization in infants with HPeV CNS infection [21].