J Infect Chemother 23 (2017) 419–426

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Review Article

Human parechovirus type 3 infection: An emerging infection in neonates and young infants

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ARTICLE INFO

Article history:
Received 13 April 2017
Accepted 20 April 2017
Available online 13 May 2017

Keywords:
Human parechovirus type 3
Neonates
Infants
Sepsis
Meningoencephalitis
Antibody

ABSTRACT

Human parechoviruses (HPeVs) are RNA viruses that have characteristics similar to those of enteroviruses and usually cause mild respiratory or gastrointestinal symptoms. Human parechovirus type 3 (HPeV3), first reported in 2004, is exceptional because it can provoke sepsis and meningoencephalitis leading to neurological sequelae, and even death, in neonates and young infants. Pediatricians and researchers are increasingly aware that HPeV3 is responsible for serious disease in neonates and young infants. Retrospective studies and several reports of epidemics of HPeV3 infection have provided data on epidemiology, clinical symptoms and signs, laboratory findings, and outcomes. However, the pathogenesis of HPeV3 infection remains unclear, which explains the lack of specific antiviral therapy and effective prevention measures. Maternal antibodies are important in protection against severe HPeV3-related disease, and this may be a clue regarding its pathogenesis. HPeV3 epidemics are likely to continue, and because the clinical manifestations of HPeV3 are severe, determining the pathogenesis of HPeV3 infection and establishing specific antiviral therapies are important goals for future research.

Contents

Abbreviations: PCR, polymerase chain reaction; EV, enterovirus; HPeV, human parechovirus; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin.

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http://dx.doi.org/10.1016/j.jiac.2017.04.009
1341-321X/

1. Introduction

Identifying the causative pathogen in febrile children is important, especially among neonates and infants younger than 3 months, because they have a higher risk of serious bacterial infection [1]. Despite the introduction of effective interventions, such as intrapartum antibiotic prophylaxis against *Streptococcus agalactiae* and vaccination against *Streptococcus pneumoniae* and *Haemophilus influenza*e type b, the rate of bacteremia in this population remains high: 2.2% in infants aged 1 week to 3 months in the United States [2].

Rapid viral testing with a rapid antigen test and/or polymerase chain reaction (PCR) assay can help rule out serious bacterial infection [1]. It can also reduce inappropriate use of antibiotics, a key aspect of antibiotic stewardship programs in the era of antibiotic resistance [3]. Enterovirus (EV) infection is one of the most successful targets, and use of a PCR assay reduced unnecessary diagnostic and therapeutic interventions [4]. In addition to EV infection, human parechovirus (HPeV) infection, especially HPeV type 3 (HPeV3), is now recognized as an important disease among infants younger than 3 months [5], because of its severity [6–8] and epidemiological characteristics [9–11]. Since the first report of HPeV3 detection, in 2004 [12], clinical findings have accumulated and HPeV infection now attracts considerable attention among pediatricians [13]. This article reviews the current understanding of HPeV infection in children, particularly among neonates and infants younger than 3 months.

2. Biology of HPeVs

HPeVs are small, non-enveloped, single-stranded, positive-sense RNA viruses of the genus *Parechovirus* in the family *Picornaviridae* [14]. This large family contains many important human pathogens, such as poliovirus, the coxsackie viruses, enterovirus 71, the rhinoviruses, and hepatitis A virus. Previously, the *Parechovirus* genus contained 2 species, *Human parechovirus* and *Ljungan virus*, which infects rodents [14]. The present classification comprises *Parechovirus A* (the former *Human parechovirus*) and *Parechovirus B* (the former *Ljungan virus*). Sebokele virus 1 from rodents and ferret parechovirus are being evaluated as potentially new species: "*Parechovirus C*" and "*Parechovirus D*", respectively [15].

The term parechovirus combines the prefix "para-" (similar to) and "echovirus". In fact, HPeV type 1 (HPeV1) and HPeV type 2 (HPeV2) were isolated as echovirus 22 and echovirus 23, respectively, during a summer outbreak of diarrhea in the United States, more than 50 years ago [16]. With advances in molecular biology, sequence analysis revealed a significant difference in the echovirus 22 genome, which led to reclassification as HPeV1 [17]. Parechovirus proteins differ from those of other picornaviruses and exhibit no greater than 30% amino acid identity [14]. The HPeV genome is approximately 7300 bases in length and encodes a single polyprotein, which is later cleaved by the viral protease (3C) into 3 structural proteins (VP0, VP3, and VP1) and 7 nonstructural proteins (2A–2C and 3A–3D) [18,19]. Unlike other picornaviruses, cleavage of VP0 into VP2 and VP4 does not occur in parechoviruses. Additionally, because the parechovirus 2A protein is unlikely to have protease activity [21], parechoviruses do not shut off host cell protein synthesis during replication [20]. Antisera against the N-terminal region of the VP0 protein and the C-terminal region of the VP1 protein have neutralizing activity. Of note, the C-terminal region of the VP1 protein contains the arginine-glycine-aspartic (RGD) motif [19].

3. Association of HPeV types and clinical presentation

3.1. HPeV genotypes

The HPeVs are classified into 16 genotypes based on phylogenetic analysis of the VP1 sequences [13,15]. Recently, the picornavirus study group taxonomically classified a 17th genotype [22], which was detected in a stool sample from a healthy 9-month-old girl from Côte-d'Ivore [23]. Furthermore, a new genotype was proposed in a study of fecal samples from Thai children with diarrhea [24]. The phylogenetic tree of the VP1 region sequences for the 17 HPeV types, and the 1 unclassified type, are shown in Fig. 1. The HPeV1–6 strains are isolated as viable viruses; HPeV7–17 and the 1 unclassified virus strain are identified as viral RNA.

HPeV1 is the most frequently detected virus, followed by HPeV3 and HPeV6, depending on the year and screening method [19]. Fig. 2 shows the numbers of HPeV genotypes detected by a group of regional laboratories in Japan. However, active, nationwide disease surveillance is not yet well organized in Japan. Most samples are obtained from non-sterile sites, such as stool and the nasopharynx [6]. Although HPeV1 circulates every year, HPeV3 epidemics have occurred every 2 or 3 years, since 2006, and peak during summer [6,11,25,26]. In Europe, HPeV3 epidemics occur every even-numbered year [5,9]. In Japan, HPeV2 and HPeV4 are infrequently detected [27–29]; HPeV4 is detected more frequently in Europe [13,30].

3.2. HPeV1 and clinical symptoms

HPeV infection is associated with a wide variety of clinical presentations, from asymptomatic infection or mild disease to severe disease [13]. Clinical symptoms are related to HPeV genotype and patient age [31–33]. Generally, HPeV infection causes mild respiratory or gastrointestinal symptoms [19]. HPeV1, the most frequently detected virus among HPeVs, is often found in pediatric clinic stool samples from patients with acute gastroenteritis [34]. In Finland, HPeV1 seroprevalence increased with age, and 72/79 (91%) individuals older than 1 year were seropositive [35]. Similarly, in Japan, seroprevalence of and geometric mean titer to HPeV1 increased with age and reached approximately 91% at age 3 years, a younger age as compared with HPeV3 and HPeV6 [33]. In addition, HPeV1 was mainly isolated from patients aged 6–11 months (56%) [33], suggesting that HPeV1 infection is common during infancy.

3.3. HPeV3 and clinical symptoms

Consensus opinion regarding HPeV infection has changed dramatically since the discovery of HPeV3 [19]. The first HPeV3 strain was isolated in 1999 from a stool sample of 1-year-old