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BRIEF REPORT

Human parechovirus-3 infection in a neonate with fever and suspected sepsis☆

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Abstract The human parechovirus (HPeV) are viruses of the recently described *Picornaviridae* family and are causing several infections in young children. The pathology associated with these viruses is beginning to emerge. The HPeV type 3 has been described particularly in association with sepsis-like febrile syndromes, meningitis and encephalitis in very young infants and neonates. We report the case of a 14-day-old girl with a fever and clinical sepsis that required hospitalisation and in which HPeV-3 was identified in the cerebrospinal fluid. The blood, urine and cerebrospinal fluid bacterial cultures were negative, and the patient improved.

This case illustrates the usefulness of investigating parechovirus infection in neonates with fever or suspected sepsis.

PALABRAS CLAVE
Parechovirus;
Fiebre;
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Infección por parechovirus 3 en un neonato con fiebre y sospecha de sepsis

Resumen Los parechovirus humanos (HPeV) son virus de la familia *Picornaviridae* recientemente descritos y causantes de numerosas infecciones en niños pequeños. La afección asociada a estos virus se está empezando a conocer. El HPeV tipo 3 se ha descrito especialmente asociado a síndromes febriles, sepsis-like, meningitis y encefalitis en lactantes muy pequeños y neonatos. Presentamos el caso de una niña de 14 días de vida con un cuadro de fiebre que

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precisó hospitalización por sospecha de sepsis y en la que se identificó en líquido cefalorraquídeo un HPeV-3. Las pruebas analíticas (leucocitos, fórmula diferencial y procalcitonina en sangre) fueron normales. Los cultivos bacterianos de sangre, orina y líquido cefalorraquídeo fueron estériles. La paciente evolucionó favorablemente.

Este caso ilustra la utilidad de investigar la infección por parechovirus en los recién nacidos con fiebre o sospecha de sepsis.

Introduction

Human parechoviruses (HPeV) are RNA viruses belonging to the *Picornaviridae* family. Sixteen distinct types of HPeV have been described to date. HPeV type 1 and 2 were described over 50 years ago as *Echovirus* 22 and 23, respectively, as members of the *Enterovirus* (EV) genus. Genome sequencing of these viruses in the 1990s showed that there were considerable genetic and biological differences between them and the rest of the EVs, so they were reclassified into a new genus, *Parechovirus*. The rest of the types were identified more recently.[1,2]

HPeV infections are prevalent in children under 3 years of age (60–70% of patients belong to this age group) and, by the age of 5, it is common for children to have been infected by one or more of these types. They have been associated with respiratory disease and mild gastroenteritis, as well as with meningitis, encephalitis, and neonatal sepsis.[3–5] According to recent studies, HPeV-3 may be one of the main causative agents of sepsis-like disease in infants in Europe.[6,7]

Fever without a source or febrile syndrome in very young infants less than 3 months of age poses challenges in diagnosis and treatment that have prompted many studies and different approaches. In the youngest patients it requires numerous diagnostic tests and admission to hospital, and intravenous antibiotic treatment is often given until severe bacterial infection is ruled out. Unfortunately, there are many instances in which an aetiological diagnosis of these episodes is not made.

In this paper we present a case of sepsis-like febrile syndrome in a newborn associated with the detection of HPeV-3 in the cerebrospinal fluid (CSF), and review the most important data published to date.

Clinical case

Female infant, 14 days old, who was brought to the emergency room with a fever (axillary temperature of 38.8 °C) lasting 6 h. There was no associated coughing, respiratory difficulty, vomiting, or refusal to feed. Her two-year-old sister had cold symptoms. The pregnancy had been monitored and normal. Maternal serology during gestation was normal (positive for rubella). The baby was delivered by Caesarean section due to breech presentation at 37 + 4 weeks of gestational age. She did not require resuscitation and was discharged without incident. She was exclusively breastfed. The physical examination showed no signs of pathology, other than irritability, which calmed down when the infant was held, and mottled skin with normal peripheral perfusion with capillary refill time <3 s. Auscultation of lungs and abdomen was normal, and the fontanelle was normotensive. The complementary examinations included a complete blood count, which was normal (haemoglobin 11.6 g/dL, haematocrit 34.8%, 6270 leukocytes/mm^3 with 56% neutrophils), and the platelet count of 404,000 was the only thing that stood out. The basic metabolic panel was normal, with a negative procalcitonin level (0.2 ng/ml). We collected samples for urine, blood, and CSF cultures (with negative cytochemical tests), all of which turned out negative. Molecular methods of nucleic acid amplification were used for virological diagnosis, performing direct testing of CSF for neurotropic herpesviruses (HHV-1, HHV-2, VZV, HHV-6), EV, and HPeV. The clinical sample tested positive for HPeV, and was typed as serotype 3. The baby was admitted to the hospital and given empiric antibiotic therapy for suspected sepsis for 6 days, until the culture results came out negative. She had a fever for a further 2 days (peak temperature of 38 °C) and low-grade fever the third day. She was subsequently asymptomatic. All vitals were normal at all times, as was the physical examination. She neither has rashes nor skin lesions during her hospital stay.

Discussion

HPeV infections are starting to be described widely in children around the world. The best-known genotypes are HPeV 1 and 2, which have been associated with mild respiratory infections and gastroenteritis.[4,8] Our group has described a prevalence of 3.6% for HPeV infections in children hospitalised with a respiratory tract infection, with type 1 being the most frequent.[9] At present, few clinical data associated to HPeV-4 through 16 have been published. However, HPeV-3 infections have been described in clear association with infections of the central nervous system and sepsis-like illness in newborns and young infants.[10,11] In fact, a very recent study of Sharp et al. in Kansas[12] found that up to 17% of CSF samples in children younger than 18 years analysed between June and October corresponded to HPeV infections, with HPeV-3 being the predominant type (77%). All infants were younger than 5 months and HPeV infections were more

frequent than EV infections (14%) during the same period. The main symptoms in these infections are fever and irritability, and it has been found that compared to EV infections, the fever is higher and lasts longer (2.7 days on average), the absence of pleocytosis in the CSF is more common, and the white blood cell count is lower. Some children require admission to intensive care units, but the prognosis is generally good. However, deaths have been reported in some cases,[13] with encephalitis being the main complication leading to sequelae. Between 50 and 100% of the described cases are associated with erythematous exanthema of the extremities, especially of palms and soles, which is not always present at the onset, but develops during disease progression, which could be highly indicative of HPeV infection in newborns and very young infants with fever.[14] The described duration of the exanthema is 2–3 days. However, this figure is not consistent in the literature, as it may have been overlooked in some cases, or prevalence may vary depending on the area.

In Europe, these infections are more frequent in spring and summer, as also happens with EVs,[15,16] but prospective studies are needed to confirm this seasonal distribution.

Our patient showed the typical clinical features of HPeV-3 infection, which may be quite frequent in newborns and young infants with fever.

To summarise, we could say that very young infants with fever and no other associated symptoms or with erythematous palmoplantar exanthema, with no leukocytosis, and no pleocytosis in the CSF, particularly in the spring and summer, may have an HPeV-3 infection. In these cases, performing the polymerase chain reaction on CSF or even blood could identify the aetiological agent and prevent prolonged hospital stays and unnecessary treatments.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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