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Case report

Parechovirus neonatal sepsis and meningitis – a (still) poorly recognised agent

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Abstract

Human parechovirus (HPeV), a *Picornaviridae* virus, is a microorganism associated with respiratory and gastrointestinal infections, in most cases with a benign clinical course. However, some serotypes have been recently associated with a more serious clinical outcome in young children, namely sepsis-like disease and meningitis.

In this report, we describe the case of a previously healthy, 11-day-old infant in our Paediatric Emergency Department who presented with high fever, irritability and poor feeding. No other accompanying symptoms, such as respiratory, gastrointestinal or urinary, were shown by the patient. Family history unveiled an 18-month-old sibling with an upper respiratory tract infection. Physical examination was unremarkable. Laboratory testing revealed a normal total white cell count with lymphopenia and a maximum C-reactive protein value of 21.4 mg/L. Cerebrospinal fluid (CSF) analysis showed pleocytosis with high proteinorrachia and normal glycorrhachia. With the clinical suspicion of sepsis, she was hospitalized for clinical surveillance, and empirical antibiotics were administered. Although the bacteriological exams of blood and CSF were negative, RNA of an HPeV was detected in the CSF. She had a favourable clinical course, the cerebral ultrasound was normal, and the clinical follow-up showed adequate psychomotor development until today (18 months old).

Recent publications suggested HPeV as one of the major agents of neonatal sepsis and meningitis. Similarly, several other studies reported significant neurological impairments in infants with HPeV infection. In line with these recent findings, we believe this clinical case further supports the need for more extensive research in viral aetiology and in particular of this, not so uncommon, agent in order to avoid unnecessary and potentially harmful interventions in newborns presenting with a sepsis-like clinical picture.

Keywords

Fever without a source, neonatal meningitis, parechovirus, newborn, infant, *Picornaviridae*.

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Introduction

Human parechovirus (HPeV) is an RNA virus, recently described as a member of the *Picornaviridae* family. As part of the enterovirus family, these viruses share their biological, epidemiological and clinical features. Mostly associated with respiratory and gastrointestinal infections, this agent usually presents a benign, self-limited clinical course in infants younger than 3 months of age [1-3]. However, a few serotypes, such as HPeV3, have been found to lead to more serious diseases in newborns and small infants, such as sepsis-like febrile illnesses, meningitis and encephalitis [2]. However, although most cases have a favourable clinical outcome [4], a few have shown long-lasting neurologic impairment [5].

Case report

We present the case of an 11-day-old female newborn, from an unremarkable gestation of 41 weeks, with normal obstetric ultrasounds and negative serology tests for human immunodeficiency virus (HIV), hepatitis B and syphilis and immunity for rubella and cytomegalovirus (CMV). Group B *Streptococcus* search in vaginal and rectal swabs was negative. The membrane rupture was spontaneous at 2 and a half hours before delivery. It was a eutocic delivery with an Apgar score of 9/10/10. The birth somatometry was in the 50th percentile (weight: 3,350 g, length: 49.5 cm, head circumference: 34.6 cm). There were no infectious risk factors or complications in the early neonatal period (the congenital cardiopathy screening, auditive screening and the red reflex eye screening were negative). The patient was exclusively breastfed with an adequate weight gain and length progression.

The newborn was brought to the Paediatric Emergency Department in the fall of 2018 for a single fever spike of 39.1ºC rectal temperature, accompanied by irritability during fever and poor feeding. No respiratory, gastrointestinal or urinary symptoms were displayed. Family history unveiled an 18-month-old sibling with an upper respiratory tract infection.

Upon physical examination, without fever, the newborn presented with good general appearance, unlaboured breathing, normal skin colour with no skin lesions; normotensive anterior fontanelle, adequate muscle tone and level of alertness, no abnormal eye movements, normal cardiopulmonary auscultation; the weight was in the 50th-85th percentile, and the remaining physical examination showed no alterations.

Laboratory workout showed a normal haemoglobin value (16.9 g/dL), with 5.18 x 10^{18}/L erythrocytes, haematocrit of 50.5% and medium globular volume of 98 fL; 6,260/mcL leucocytes, 3,720/mcL (59.4%) neutrophils, 1,220/mcL (19.5%) lymphocytes (with the identification of atypical lymphocytes in the blood smear analysis), 232,000/mcL platelets. The C-reactive protein (CRP) was 14 mg/L and the renal analysis (urea 12 mg/dL; creatinine 0.25 mg/dL) and ionogram (Na: 130 mmol/L; K: 5.4 mmol/L; Cl: 96 mmol/L) were normal. A blood culture was performed. Arterial blood gas analysis was not performed.

During the first 24 hours of evaluation, the infant presented with fever at 9-hour intervals, maintaining otherwise a good general appearance, without other associated symptoms. The hemogram re-evaluation at 6 and 9 hours after admission was similar, and the maximum CRP value was 21.4 mg/L. No alterations were present in the urinalysis, and the urine culture was sterile. The search for viral antigens in the respiratory secretions was negative for the syncytial respiratory virus and A and B influenza virus. Cytochemical examination of the cerebrospinal fluid (CSF) showed pleocytosis (40 leucocytes/mcL), proteins of 163 mg/dL and glycorrhachia of 49 mg/dL (for a blood glucose of 80 mg/dL), although it was a traumatic lumbar puncture. Gram test and the antigen test for group B *Streptococcus* were negative.

Empirical intravenous antibiotic therapy with ampicillin and cefotaxime at meningeal dosage was initiated and stopped after 5 days, once blood and CSF bacteriological exams were revealed negative and RNA of an HPeV was detected in CSF. However, it was not possible to identify the virus

serotype. Other viruses such as enterovirus and herpes simplex 1 and 2 tested negative in the CSF.

Throughout the hospital stay, there was a clear clinical improvement, with the absence of fever after the first day. She was always hemodynamically stable, with a good general appearance, without new symptoms or signs, and she rapidly recovered the normal feeding behaviour. There were no alterations in head circumference and no other clinical complications. Cerebral ultrasounds performed on the second and sixth days were normal. The analytic revaluation on day 5 showed a normal leucogram and a negative CRP. The patient was released home after 6 days, exhibiting good clinical condition. The follow-up appointments at both 6 and 18 (present date) months showed a favourable clinical evolution with normal psychomotor development.

Discussion

We present a case of an HPeV infection in a small infant, an age with a known higher incidence of this infection [1, 2]. This case illustrates the most common features of an HPeV infection in this period of life, in particular the presentation as a sepsis-like syndrome with high fever and irritability without localization of symptoms [3, 6, 7]. According to recent publications, this clinical outcome can be more common than previously believed, with the HPeV as one of the major agents of neonatal sepsis and meningitis [7]. In particular, in the United Kingdom it has been shown that the incidence of HPeV or enterovirus infection is more than 2 times higher than bacterial meningitis [5].

The epidemiological context of the presented case is consistent with current evidence demonstrating that the HPeV infections are more frequent in the summer or fall. Also, the familial contact with an infant sibling with an upper respiratory infection further supports the referred etiology, as HPeV is frequently responsible for non-severe respiratory and gastrointestinal infections in infants below 3 years of age (about 60-70% of cases occur in children of that age) [1, 6].

HPeV infections present with fever, usually higher than in cases of enterovirus infection, and irritability. Despite a completely normal initial physical examination, in more than half of the cases an erythematous exanthema of the extremities (without sparing of palms and soles) may appear approximately 2 to 3 days after the initial symptoms [1, 3, 8]. Our newborn did not present with exanthema.

Laboratory results of HPeV infections, compared with enterovirus infection, usually display lower leucocyte counts together with a silent CSF cytochemical exam, often with no pleocytosis [2, 9]. In the described case, the CSF exam showed pleocytosis with a negligible elevation of protein levels but normal glucose levels. However, these values should be taken into account in the context of a traumatic lumbar puncture.

The fact that the HPeV meningitis often presents with normal leucogram and CRP and a CSF without significant changes, may lead to a poor investigation. In the majority of cases, the HPeV virus cannot be detected in the CSF, but only on peripheral sites, when stool samples or respiratory secretions are analysed [5]. Thus, the actual incidence of HPeV infection might be an underestimation of reality, leading to prolonged hospitalizations and antibiotic therapy [7]. In our case, for instance, the newborn was submitted to unnecessary antibiotic therapy due to suspicion of bacterial sepsis/meningitis, a frequent situation with newborns, who are characteristically oligosymptomatic.

Our newborn did not show any initial complications due to the infection and had favourable clinical evolution, with normal psychomotor development. Irrespective of presenting mortality and morbidity inferior to 1%, several studies reported significant neurological sequelae in infants with HPeV infections, particularly with HPeV3 [5]. Despite the lack of studies, the potential of HPeV to lead to permanent neurological deficits is known, leading some authors to recommend formal psychomotor surveillance in the cases of neurologically severe presentations, persistent symptoms and neuroimaging alterations in the acute phase of the disease [2, 5, 6].

With this case, we intend to highlight the importance of better dissecting and addressing viral infections, in particular HPeV, when proceeding with differential diagnosis of serious disease in the neonatal period. In this case, we suspected a viral etiology for several reasons: the newborn did not have any risk factors in the delivery or neonatal period; there was a history of an 18-month-old brother with upper respiratory symptoms, and despite the single febrile spike accompanied by irritability and

feeding difficulties, outside the febrile period, she was a newborn with a good general state, without prostration, irritability or other signs of sepsis and the physical examination did not show any alterations. In our opinion, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for viruses in the CSF should be considered in these situations, according to the epidemiological context and the potential indication for specific therapies (herpesvirus).

Regarding limitations in the course of this case, we point out the absence of virus serotyping and the lack of lactate measurement in CSF (a sepsis biomarker that could have been useful to differentiate between acute bacterial and viral meningitis) [10, 11].

In conclusion, more adequate and accurate diagnosis in these cases would then allow for improvement in empirical diagnostic and therapeutic interventions as well as avoidable inappropriate antibiotic treatments and reduction in prolonged hospitalizations.

Declaration of interest

The Authors declare that there were no conflicts of interest in conducting this work. The Authors received no financial support for the research, authorship, and/or publication of this article.

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