Parechovirus infection: a rare cause of neonatal encephalitis
Truant AS, Fischer-Fumeaux CJ, Truttmann AC, Heiniger C, Llor J, Rosato L, Faignart N, Asner S, Matthias Roth-Kleiner M, Clinic of Neonatology (TAS, FCJ, TAC, RKM), Pediatric Neurology Unit (FN), Pediatric Infectiology Unit (AS), Department Woman-Mother-Child, University Hospital and University of Lausanne, Lausanne, Switzerland, Department of Pediatrics (HC, RL), Hôpital Neuchâtelois, Neuchâtel, Switzerland, Department of Pediatrics (LJ), Cantonal Hospital of Valais, Sion, Switzerland

Title figure:
Human parechovirus type 3 (source: www.nature.com).
Human Parechovirus (HPeV) infections show a variety of clinical manifestations. Infections in early childhood are often severe, mostly leading to sepsis and/or meningitis. As Enterovirus (EV), Parechovirus belongs to the family of Picornaviridae. Their clinical and morphological properties are similar. However, HPeVs were shown to be distinct from EVs and other Picornavirus groups in several features of their genome organization, structure and replication.

While EVs are found in individuals of all ages, HPeVs mainly infect children under 5 years of age, especially young infants. Neonatal presentations are less well described and recognized. We present two patients with neonatal encephalitis.
This female infant was born in a regional hospital at 38 0/7 weeks of gestation after a pregnancy complicated by gestational diabetes. She developed respiratory distress, which resolved after 72 hours of CPAP and was felt to be consistent with transient tachypnea of the newborn and lung immaturity. On day of life 7, her condition again deteriorated with fever (up to 39.1°C), followed by irritability and central apnea with desaturations two days later. She was put on CPAP, antibiotics were started, and she was transferred to the level III referral center.

A complete blood count and CRP were within normal limits. EEG and cerebral function monitoring (CFM) were normal without evidence of seizures. Examination of cerebrospinal fluid (CSF) showed no pleocytosis, normal protein and glucose concentrations; however, PCR was strongly positive for Parechovirus (negative for Enterovirus).

On day of life 15, an MRI showed multiple punctiform lesions of the periventricular white matter on T2-weighted images, corresponding with cytotoxic lesions on ADC maps (Fig. 1, 2). Fortunately, at 9 months of age, the infant displayed normal neurodevelopment. A follow-up MRI was not obtained.
Fig. 1

MRI of patient 1: multifocal punctiform lesions in the perventricular white matter (left: T2-weighted image; right: ADC mapping).
MRI of patient 1: multifocal punctiform lesions in the periventricular white matter (left: T2-weighted image; right: ADC mapping).
Of note, this infant was born during the summer season and had a 2 6/12 year-old brother. However, at the time of her birth, both her parents and her brother were healthy with no evidence of any contagious diseases.
This male infant was born in a regional hospital at 32 6/7 weeks of gestation and adapted well with Apgar scores of 8, 9, and 10 at 1, 5, and 10 minutes, respectively. Pregnancy had been remarkable for spontaneous twins with intrauterine fetal demise of one twin at 8 weeks of gestation. His initial hospital course was unremarkable and he was discharged home on day of life 20 at a corrected gestational age of 35 5/7 weeks. Two days later, he was re-hospitalized because of feeding difficulties, hypotonia and apnea requiring mechanical ventilation. He was transferred to the level III referral center.

Except for a left shift, both a complete blood count and CRP were normal. He had a normal EEG. Examination of cerebrospinal fluid (CSF) showed no pleocytosis, normal protein and glucose concentrations; however, PCR was positive for Parechovirus.

On day of life 27 (at a corrected gestational age of 36 5/7 weeks), an MRI showed bilateral punctiform lesions of the periventricular white matter on T2-weighted images, corresponding with cytotoxic lesions on ADC maps (Fig. 3); in addition, a cystic right parietal subcortical cystic lesion was identified (Fig. 4) and interpreted as the consequences of an antenatal ischemic stroke.
MRI of patient 2: bilateral multifocal punctiform lesions and cytotoxic edema in the posterior periventricular white matter (left: T2-weighted image; right: ADC mapping).
MRI of patient 2: cystic subcortical lesions in the right parietal region felt to be due to an ischemic antenatal stroke (T2-weighted image).
On follow-up at 6 months, monoparesis of the left arm was noted. Two months later, this finding had improved with physiotherapy. At the same time, an MRI examination again documented the subcortical lesion, however, the periventricular white matter lesions had resolved.

Of note, this infant was also born during the summer season. He had no siblings, and both his parents were healthy with no evidence of any contagious diseases.
HPeV is part of the Picornaviridae family (1). In humans, 16 subtypes are known (Fig. 5) (2). Subtypes 1 and 3 are most frequent in Europe and the United States. Infections with HPeV are often asymptomatic or manifest with only minor respiratory or digestive diseases.

However, in young infants, HPeV-3 is known to cause severe infections (1, 3). Transmission of the virus is mainly by fecal-oral route, via the respiratory tract or transplacentally. Despite the paucity of literature on the topic, it is important to perform HPeV RT-PCR on the placenta and on maternal blood to document vertical transmission.
Classification of Picornaviridae

(HPeV: human Parechovirus).
Clinical manifestations vary accordingly to biological characteristics of the different subtypes. HPeV-3 in particular is known to induce neurological signs like hypotonia, irritability, drowsiness and seizures. Other symptoms include fever, apnea, abdominal distension, diarrhea, rash and sepsis. It may be a cause of sudden infant death syndrome (1, 2).

The neuropathogenicity of HPeV-3 is due to its unique receptor that allows faster replication in the central nervous system and results in pre-oligodendrocyte and axonal lesions. It is stipulated that after infecting the neurons, HPeV-3 might activate a toll-like receptor (TLR 8) in the cell body, especially in the developing axon and its growth cone, which then results in an axonal retraction and neuronal apoptosis (2). Repeated MRI examinations may document extensive white matter loss and severe gliosis in the white matter remote from the acute phase lesions (4).

The prevalence of EV and HPeV viremia in children less than three years of age is largely underestimated (9). Typically, blood tests show only moderate or even absent inflammatory signs and normal or low leucocyte counts. On CSF examination, there is typically no pleocytosis and cerebrospinal fluid protein and glucose levels are normal (3). The diagnostic gold standard is PCR in blood, CSF or stools (2). EEG is often normal but subclinical epileptic discharges are reported.
Cerebral ultrasound is normal or may show periventricular echodensities. MRI may typically reveal necrotic lesions in the periventricular and subcortical WM similar to what can be seen with Enterovirus infections, particularly in newborns and young infants (4, 5). The severity of imaging abnormalities seems to correlate with later neurodevelopmental outcome (4). In our cases, multiple periventricular white matter echodensities corresponding to cytotoxic edema were observed. On repeat MRI in case 2, the periventricular T2-lesions had disappeared by 8 months of age, but enlarged ventricles were noted, suggesting slight to moderate loss of substance (images not shown).

Risk factors are still debated. Breastfeeding seems to be protective, but with advancing maternal age, maternal antibody titers fall. At birth, concentrations of maternal antibodies against HPeV-1 are higher than against HPeV-3 (6). Having an older sibling (< 2 years) seems to increase the risk and severity of HPeV-3 infection due to increased viral transmission in the confined space of the family (7). Prognosis of children with HPeV encephalitis is uncertain. Neurodevelopmental outcome may be impaired and sequelae like behavioral disorders, impaired motor skills, deafness, visual disorders, or cerebral palsy have been reported (8). Therefore, follow-up of newborn and young infants after HPeV encephalitis is mandatory, and one should be cautious about their prognosis. Having a discontinuous background and repetitive seizures on
amplitude-integrated EEG is associated with poorer prognoses (4).

So far, no specific treatment is available. Research is ongoing on the efficacy of pleconaril, a capsid inhibitor, and the use of immunoglobulins (2). Prevention plays a key role, particularly in NICUs with strict adherence to standard measures of hand hygiene.
Both HPeV and EV may cause severe disease in the neonatal period. Because of the similarity in clinical presentation, neonates presenting with sepsis-like illness with fever, irritability and seizures should be evaluated for possible EV and HPeV infections, particularly when a bacterial cause is not probable or has been excluded. Rapid diagnosis of EV or HPeV infection can reduce exposure to unnecessary antibiotic therapy.

Normal findings on routine CSF examinations (cell count, protein and glucose concentrations) do not exclude Parechovirus encephalitis; HPeV PCR is required. Neurological follow-up is essential in children after HPeV encephalitis. In case of HPeV or EV encephalitis in the neonatal period, cerebral MRI should be part of the diagnostic work-up, particularly in infants who present with seizures, apnea, hypotonia and/or abnormal EEG background activity. The best timing for MRI is between 3 – 5 days after the onset of symptoms.
REFERENCES


