



Case Report

Human parechovirus type 5 neurological infection in a neonate with a favourable outcome: A case report



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ARTICLE INFO

Article history:

Received 28 August 2019

Received in revised form 3 October 2019

Accepted 3 October 2019

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:

Neonatal infections

Human parechovirus type 5

CSF

Molecular characterization

CNS infection

Phylogenetic analysis

ABSTRACT

The majority of parechovirus A type 5 (PeV-A5) infections have been reported in patients with gastrointestinal syndromes. In contrast, a sepsis-like illness associated with PeV-A5 infection has been reported only anecdotally. Herein, we report the first case in Italy of a PeV-A5 neurological infection presenting in a neonate with a sepsis-like syndrome. The patient, a healthy male infant born at 41 weeks of gestation, was highly distressed and inconsolable, and had been crying persistently, with poor breastfeeding, since the previous day. From day 2 to day 4, the newborn was feverish with mild irritability; breastfeeding was preserved and regularly supported. His clinical condition progressively improved, with defervescence on day 4. He was discharged after 7 days, and neurological examination results indicated only mild impairment in visual fixation and vertical eye tracking and mild axial hypotonia. The Italian PeV-A5 strain was phylogenetically related to three strains detected in Denmark in 2012, as well as to one detected in Australia and one in Greece in 2015, with an average nucleotide identity of 97.9% (range 95.9–100.0%). Enterovirus/PeV infection in the newborn should be ruled out in cases of infants with unexplained fever and/or a sepsis-like syndrome and/or meningoencephalitis. An aetiological diagnosis is essential to avoid the unnecessary administration of antibiotics and to plan long-term follow-up until schooling.

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Introduction

Parechovirus A (PeV-A) is an increasingly recognized cause of meningo-encephalitis in children, and PeV-A type 3 (PeV-A3) is thought to be particularly neurotropic, as it is frequently identified in the cerebrospinal fluid (CSF) of infants with sepsis-like presentations (Wolthers et al., 2008; Harvala et al., 2010). In contrast, the large majority of PeV-A type 5 (PeV-A5) have been identified in stool samples of patients with gastrointestinal syndromes (Graul et al., 2017; Pajkrt et al., 2009; van der Sanden et al., 2008; Zhang et al., 2011; Zhong et al., 2011). Indeed, PeV-A5 has seldom been reported as a cause of meningo-encephalitis or sepsis-like syndromes (Cabrerizo et al., 2015). Herein, we report the first Italian case of PeV-A5 neurological infection observed in a neonate with a sepsis-like syndrome.

Case report

A healthy male infant, born by vaginal delivery in November 2018 at 41 weeks of gestation, presented at 15 days old to the emergency room of F. Del Ponte Hospital in Varese. The newborn was highly distressed and inconsolable, and had been persistently crying, with poor breastfeeding and a low-grade fever (37.6 °C) since the previous day. There had been contact with an older sister suffering from otitis. He was admitted without any respiratory or gastrointestinal signs and symptoms. His vital signs were stable, with HR 130 ppm, RR 40 bpm, and pulse oximetry 99%. As summarized in Table 1, laboratory tests on admission revealed a slight increase in C-reactive protein (CRP) level (13.2 mg/l), mild leukopenia with marked relative monocytosis (white blood cell count $4.55 \times 10^9/l$, with monocytes 24%, neutrophils 34%, lymphocytes 41%), normal haemoglobin level, and normal platelet count. Blood and urine samples were collected for culture and analysis and the baby was admitted to the neonatal intensive care unit (NICU).

Soon after admission, he became whiny and developed a high fever (39 °C), in addition to a high heart rate (200 bpm at rest), with

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Table 1
Clinical findings, laboratory testing, and other investigations performed during the 7 days of hospitalization.

Follow-up (days)	Signs and symptoms ^a	Laboratory testing	Other investigations
0 ^b	Irritability +++ Fever ++ Fussing ++ Persistent crying ++ Difficulty in feeding ++ Axial hypotonia +	Leukocyte count 4.4×10^9 cells/l, with N 34%, L 41%, Mo 24%; Hb 16.2 g/dl; PLT 419×10^9 cells/l; CRP 13.8 mg/l CSF, clear colourless appearance; glucose 52 mg/dl; total protein 49 mg/dl; cells absent Faecal antigen assays (rotavirus, adenovirus, norovirus, astrovirus, sapovirus): negative Blood, urine, and CSF: sent for culture	
1	Fever ++, Irritability ++, Plaintive crying +	CRP 12.9 mg/l	Negative cranial ultrasound
2	Fever +	HSV types 1 and 2 DNA in CSF: negative Urine culture: negative	
3	Fever +		
4	Defervescence		
5	Improving, good breastfeeding	CSF culture: negative Blood culture: negative PeV real-time RT-PCR on blood: positive PeV real-time RT-PCR on CSF: positive	
6	Improving, good breastfeeding	Leukocyte count 8.62×10^9 cells/l, with N 16%, L 73%, Mo 8%; Hb 17.3 g/dl; PLT 361×10^9 cells/l; CRP 0.7 mg/l	
7 ^c	Negative neurological examination, mild impairment in visual fixation, mild axial hypotonia		

N, neutrophils; L, lymphocytes; Mo, monocytes; Hb, haemoglobin; PLT, platelets; CRP, C-reactive protein; CSF, cerebrospinal fluid; HSV, herpes simplex virus; PeV, parechovirus.

^a + Mild; ++ moderate; +++ severe.

^b Day of admission.

^c Day of discharge.

cutaneous vasoconstriction and cold extremities. Axial hypotonia was observed during a neurological examination and a lumbar puncture was therefore performed, revealing normal physical, chemical, and microscopic cerebrospinal fluid (CSF). Broad-spectrum antibiotic therapy with ampicillin and amikacin was started, as a central nervous system (CNS) disease was suspected. Intravenous acyclovir was not administered due to the negative real-time PCR for herpes simplex virus types 1 and 2 DNA in the CSF. Rotavirus, adenovirus, norovirus, astrovirus, and sapovirus faecal antigens were negative. A cranial ultrasound performed on day 1 was negative.

From day 2 to day 4, the newborn was feverish with mild irritability; breastfeeding was preserved and regularly supported. His clinical condition progressively improved, with defervescence on day 4. Antimicrobials were discontinued after blood, urine, and CSF tests came back negative.

On day 5, CSF and blood samples were sent to the Molecular Virology Unit of the Fondazione IRCCS Policlinico San Matteo, Pavia to investigate possible enterovirus and PeV infections. CSF and plasma samples were positive on human PeV-specific real-time RT-PCR assays (Nix et al., 2008). Genotyping was performed by sequencing amplicons obtained for both clinical samples using nested RT-PCR (Harvala et al., 2008). Phylogenetic analysis of the sequences obtained indicated that the infection was caused by a PeV-A5 strain. The newborn was discharged after 7 days, and neurological examination results indicated only mild impairment in visual fixation and vertical eye tracking and mild axial hypotonia. At 1 month from onset, a magnetic resonance imaging (MRI) scan was normal and there was no evidence of white matter lesions. At the first follow-up appointment in January 2019, he demonstrated normal psychomotor development with a significant recovery of visual function.

Phylogenetic analysis

A total of 21 PeV-A5 sequences retrieved from the GenBank database matched the genomic region sequenced (partial VP3/P1).

Overall, based on the maximum likelihood tree obtained, three different clades were identified (named as A–C in Figure 1). The average nucleotide identity between sequences belonging to the clade C was 87.5% (range 64.3–100.0%). However, if we focused the analysis on strains that were closely related to the Italian strains (accession numbers [MN067978–79](#)), three of them were detected in Denmark in 2012, one in Australia and one in Greece in 2015. The average nucleotide identity increased to 97.9% (range 95.9–100.0%). Significantly, it is worth noting that the vast majority of sequences were obtained from PeV-A5 strains detected in stool samples. It appears that our PeV-A5 strain is the first to be sequenced directly from CSF.

Discussion

Signs of sepsis in neonates are often non-specific and a high level of alertness is needed for early diagnosis. The introduction of PeV screening in clinical diagnostic laboratories has improved the diagnosis of PeV infections, especially in clinical samples from patients with neonatal sepsis or neurological syndromes (Harvala and Simmonds, 2009). Among PeVs, PeV-A3 is known to induce neurological signs like hypotonia, irritability, drowsiness, and seizures, and other generic signs and symptoms including fever, diarrhoea, abdominal distension, apnoea, and rash (de Crom et al., 2016). PeV infections have been reported in Italy since 2008 and the great majority of them have been due to PeV-A3 (Piralla et al., 2012; Pariani et al., 2014; Piralla et al., 2014; Bubba et al., 2017). There have been no reports of PeV-A5 circulating in Italy or of PeV-A5 in patients with sepsis-like and neurological syndromes. PeV-A5 has predominantly been detected in the stools of patients with mild gastroenteritis, along with a few retrospective cases of PeV-A5 infection that were associated with more severe syndromes (Cabrerizo et al., 2015).

In our case, PeV-A5 was detected and sequenced in both CSF and plasma samples of a patient with signs and symptoms of a sepsis-like illness, whose clinical syndromes resolved in less than 7 days,

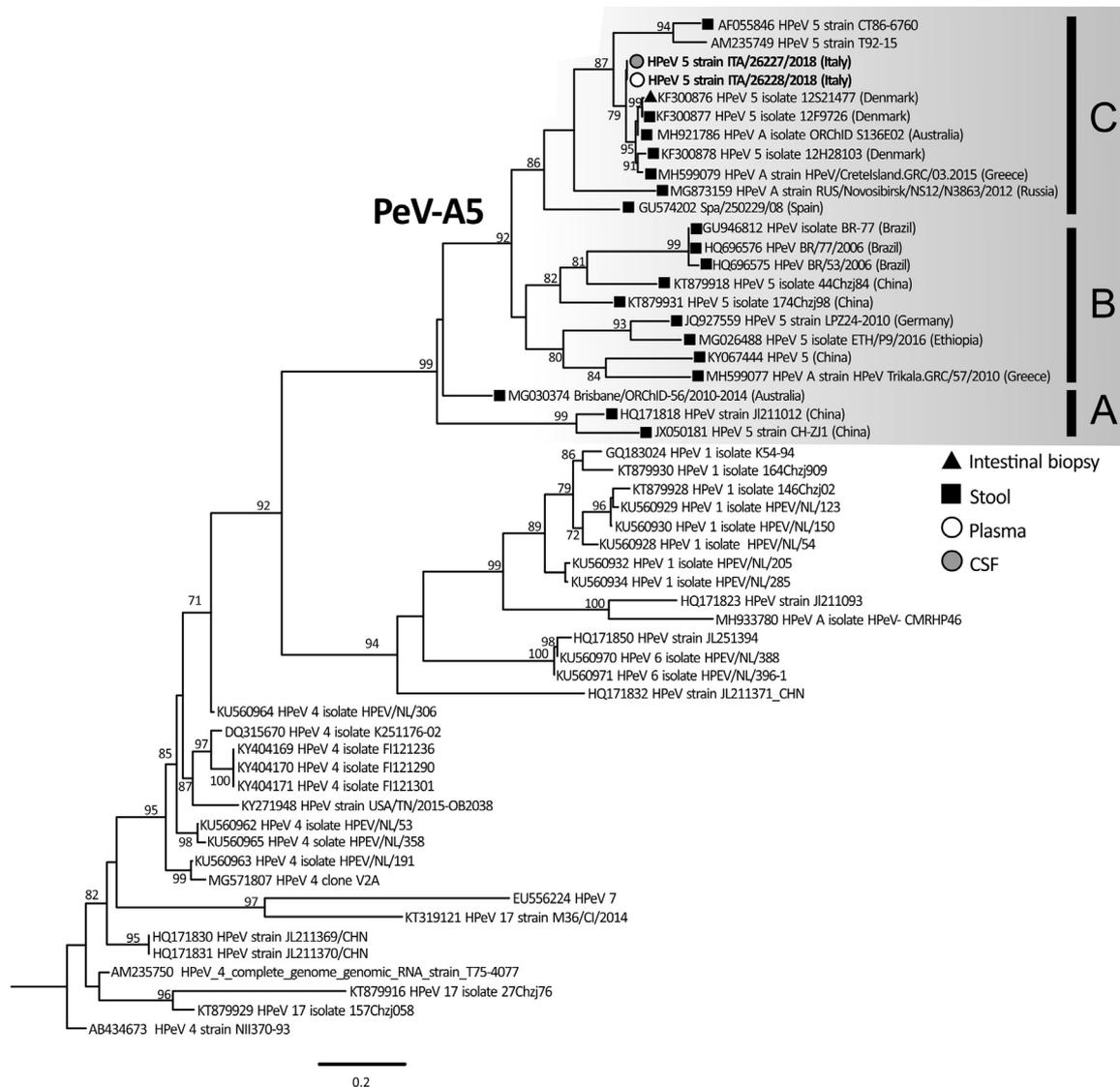


Figure 1. Phylogenetic rooted tree inferred by maximum likelihood of partial VP3/VP1 sequences (296 nt). Significant branch support values (>70%) are given for maximum-likelihood implementations (IQ-TREE bootstrap support) and are reported near the branch nodes. Strains retrieved from the GenBank database using the BLAST algorithm (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) with >75% nucleotide identity as compared to the two Italian strains (CSF and plasma) were included in the phylogenetic tree.

with a favourable outcome. Currently we cannot exclude the possible occurrence of long-term neurodevelopmental sequelae, but the full recovery of psychomotor development seems to be a good sign. Short-term outcomes are generally good, but medium and long-term outcomes of infants after PeV infections are still unknown. There are very few studies on the topic and those available are limited to small sample sizes with different methodologies (Martin Del Valle et al., 2019; Britton et al., 2016; Verboon-Maciolek et al., 2008).

In general, the prognosis is more favourable when there is no CSF injury, whereas infants with encephalitis (alterations in neuroimaging and/or seizures) are more likely to develop neurological disability and white matter injury disease (Britton et al., 2016). PeV meningoencephalitis is often difficult to identify because the clinical presentation of signs and symptoms of neurological involvement are non-specific in newborn babies and young infants. Simple detection of PeV in the CSF is not predictive of CNS disease and should not be used as a negative prognosis marker (Harvala et al., 2014). Seizures, fever, apnoea, or

prematurity appear to be risk factors for neurological sequelae, but further studies are required to confirm this (Joseph et al., 2019).

In our case, the newborn was a full-term, healthy baby and his symptoms of irritability, fever, and tachycardia were more related to the sepsis-like syndrome. CNS involvement was mild, there were no seizures, and intensive support was not needed. As previously observed in neonatal PeV CNS infections, pleocytosis or biochemical alterations in the CSF are usually absent (Black et al., 2019; Verboon-Maciolek et al., 2008). A recent study of 29 cases of PeV neurological infections showed that in all cases the CSF had less than 20 white cells per cubic millimetre (Kadambari et al., 2019). In line with these observations, all CSF parameters in our case were normal and pleocytosis was absent. Finally, rapid testing using real-time RT-PCR could be considered the gold standard for PeV diagnosis, although antiviral drugs against these infections have yet to be approved and treatment is limited to supportive care. In addition, the use of multiple clinical samples such as CSF, respiratory specimens, blood, urine, and stool specimens could improve detection rates of PeV infections.

In conclusion, PeV infection in the newborn should be ruled out in the case of an infant with unexplained fever and/or with a sepsis-like syndrome and/or meningoencephalitis. An aetiological diagnosis is essential to avoid the unnecessary administration of antibiotics and to plan long-term follow-up until schooling.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None.

Ethical approval

Approval was not required.

Acknowledgements

We would like to thank Sofie Elisabeth Midgley and Thea Kølsten Fischer for the additional information on sequencing and clinical isolates provided. We thank Daniela Sartori for manuscript editing and Sheila McVeigh for English revision.

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