Human Parechovirus Causes Encephalitis with White Matter Injury in Neonates

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Objective: To assess the role of human parechoviruses (HPeVs) as a cause of neonatal cerebral infection and to report neuroimaging findings of newborn infants with encephalitis caused by HPeVs.
Methods: Clinical presentation, cranial ultrasonography, magnetic resonance imaging (MRI) findings, and neurodevelopmental outcome of 10 infants admitted to a neonatal intensive care unit and diagnosed with encephalitis caused by HPeVs are reported.
Results: Nine of 10 infants, with a gestational age of 29 to 41 weeks, presented at 36 to 41 weeks postmenstrual age with clinical seizures. Seven had a fever and six had a rash. Clinical presentation was similar to that of infants with enterovirus infection. Cranial ultrasonography showed increased echogenicity in the periventricular white matter in all infants. Neonatal MRI confirmed white matter changes in nine infants, which changed to gliosis on later MRI. Outcome was variable with cerebral palsy in one, a suspect outcome at 18 months in one, learning disabilities at 7 years of age in one, epilepsy in one, and normal neurodevelopmental outcome in five children. Follow-up of one infant was only 9 months.
Interpretation: HPeVs should be added to the list of neurotropic viruses that may cause severe central nervous system infection in the neonatal period. White matter injury can be visualized with cranial ultrasonography, but more detailed information is obtained with MRI and especially diffusion-weighted imaging. Because clinical presentation of HPeV encephalitis is similar to that of enterovirus, real-time polymerase chain reaction for both viruses should be performed in atypical presentation of neonatal seizures. Ann Neurol 2008;64:266–273

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Neuroimaging data in neonatal enterovirus (EV) meningoencephalitis leading to severe white matter damage and adverse neurological sequelae were recently reported.[1] The infants presented with repetitive seizures associated with fever, a rash, or both.

Human parechoviruses 1 and 2 (HPeV 1 and HPeV 2) were previously known as echovirus 22 and echovirus 23, and were considered to belong to the genus *Enterovirus.* From sequence analysis, these viruses have been reclassified in the new genus *Parechovirus* in the family Picornaviridae.[2,3] Recently, four new members of this genus have been identified: HPeVs 3 through 6.[4–8] To date, HPeV 1 and HPeV 2 have not been reported as a cause of neonatal central nervous system (CNS) infection,[9] but HPeV 3 has been associated with neonatal infection presenting with symptoms of the CNS.[4,5,10] No detailed information about either clinical symptoms or imaging findings were provided in these publications.

In 2006, a reverse transcription polymerase chain reaction (RT-PCR) for HPeV has become available. We recently reported clinical data of infants with HPeV admitted to our neonatal intensive care unit (NICU) between 1998 and 2006.[11] We now describe neuroimaging data of 10 infants who presented with similar signs and symptoms as infants with EV meningoencephalitis, but in whom EV could not be detected in different clinical samples and who were now diagnosed to have HPeV CNS infection.

The aim of this study was to describe the clinical presentation, cUS data, MRI findings, and neurodevelopmental outcome of 10 neonates with HPeV-proven encephalitis.

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Patients and Methods

Between January 1997 and January 2008, fourteen infants with encephalitis were admitted to the NICU of the Wilhelmina Children's Hospital, University Medical Center (Utrecht, The Netherlands), which is a tertiary referral center. The diagnosis of EV cerebral infection was made in three infants, rotavirus was isolated from feces in one infant, and the agent of encephalitis remained unidentified in one infant. In 9 of 14 infants with encephalitis, HPeV RNA was isolated.

Of the 10 infants with HPeV encephalitis described in this study, prospective diagnosis was accomplished in four infants who presented in 2006 to 2007 with encephalitis to the NICU of the Wilhelmina Children's Hospital. Retrospective diagnosis was accomplished in the remaining six infants with heretofore unexplained encephalitis, five of whom had presented to the Wilhelmina Children's Hospital between 1998 to 2006, and one of whom presented to The Hospital for Sick Children (Toronto, Ontario, Canada) in 2006. These six infants were diagnosed retrospectively based on molecular analysis for the presence of HPeV RNA cerebrospinal fluid (CSF; four infants), blood (one infant), or feces (one infant), which had been stored at −70°C.

Cranial Ultrasonography

cUS was performed using either an ATL Ultramark 4 machine with a 7.5MHz transducer (Advanced Technology Laboratories; Philips Medical Systems, Best, the Netherlands) or a Toshiba Aplio (Toshiba Medical Systems, Zoetermeer, the Netherlands) with a multifrequency transducer.

Magnetic Resonance Imaging

MRI was performed using a 3-Tesla Intera system, a 1.5- or 0.5-Tesla Philips system (Best, The Netherlands), or 1.5-Tesla GE system. MRI included sagittal T1, axial spin-echo T2, inversion recovery, fluid-attenuated inversion recovery sequences, and diffusion-weighted imaging (DWI) including apparent diffusion coefficient mapping. Slice thickness varied between 4 and 2mm.

Neurophysiological Monitoring

Neurophysiological monitoring was performed in nine infants using continuous single or two-channel amplitude-integrated electroencephalographic (EEG) for several days.

Viral Diagnosis

The viral diagnosis was always confirmed by a positive HPeV RT-PCR on blood, CSF, stool, or nasopharynx.[5,8] Molecular typing was performed as described previously.[4,5]

Results

Clinical Data

Three preterm and seven full-term infants, of whom six were born by vaginal delivery, presented with a sepsis-like illness suggestive of a viral infection (Table 1). All bacterial cultures remained negative. The male/female ratio was 3:7. Nine of 10 infants presented with clinical seizures, and 6 of 10 were irritable. All seven of the full-term infants presented during the first 2 weeks from birth, most commonly in the first week. All three preterm infants presented several weeks after birth, after discharge home or after transfer from the NICU to the local hospital. Four infants developed mild hypotension, which was easily treated with inotropes. CSF analysis was performed in all infants, but an increased white blood cell count was seen in only one patient (188×10^6/L). Protein and glucose levels were always within the reference range.

Imaging Results

Imaging results are summarized in Table 2.

CRANIAL ULTRASONOGRAPHY.

cUS was performed several times during the first week after birth and once a week until discharge, and was initially normal in three preterm infants (Patients 1, 5, and 6). cUS on readmission (36 and 39 weeks postmenstrual age) and on admission in all full-term infants showed extensive periventricular echogenicity. Cysts developed in the periventricular white matter 2 weeks after onset of symptoms in Patient 1.

MAGNETIC RESONANCE IMAGING.

MRI performed between 1 and 14 days after onset of clinical symptoms showed diffuse high signal intensity in the white matter on T2-weighted spin-echo sequences with focal areas of low signal intensity (punctate white matter lesions), suggestive of petechial hemorrhages in four infants. DWI, performed in eight infants, showed areas of restricted diffusion in the periventricular white matter, corpus callosum, deep white matter, optic radiation, internal capsule, posterior thalami, and cerebral peduncles (Figs 1–4). Reduced apparent diffusion coefficient values were found in these areas of increased signal intensity on DWI. A repeat MRI of Patient 1 at 2 years showed extensive white matter loss and severe gliosis in the periventricular white matter. A repeat MRI of Patient 2 at 7 years showed mild periventricular gliosis in the white matter (see Fig 1). A repeat MRI of Patient 7 at 3 months showed persistent white matter lesions suggestive of gliosis (see Fig 2).

Neurodevelopmental Outcome and Relation with Imaging Data

Neurodevelopmental outcome was assessed at term, 6, 15, and 24 months after birth (corrected for prematurity), and longer in those with an adverse outcome (see Table 2). A full neurological assessment and the Griffiths neurodevelopmental scale were performed. One child experienced development of cerebral palsy, one has learning disabilities at 7 years of age, one experienced development of postneonatal epilepsy, but with a normal cognitive outcome at 3 years of age, and one shows mild distal hypertonia at 18 months.

Table 1. **Clinical, Virological, and Amplitude-Integrated Electroencephalographic Data of 10 Patients with Human Parechovirus Encephalitis**

Patient No./ Birth Date/ Sex	GA (wk)	Birth weight (gm)	Apgar Score (1′/5′)	Time of Onset of Illness (days)	Clinical Symptoms	Inotropic Support[a]	Site of Isolation of HPeV RNA	aEEG BG	Type and Duration of Seizures	Antiepileptic Treatment
1/March 1998/F[b]	28	1,100	8/9	55	Fever, hypertonia, seizures, apnea, rash	None	CSF	DNV	RS > 24 hours	Phenobarbital Lidocaine Midazolam Clonazepam
2/July 2000/F	40	3,770	8/9	6	Fever, irritability, seizures, apnea, rash	Yes	Stool	CNV	RS > 24 hours	Phenobarbital Lidocaine Midazolam Clonazepam
3/February 2002/M	39	3,360	9/9	14	Fever, irritability, seizures, apnea, rash	None	CSF	CNV	SS < 24 hours	Phenobarbital Lidocaine Midazolam
4/June 2004/F[a]	41	3,670	9/10	6	Fever, irritability, seizures, apnea, rash, diarrhea	Yes	CSF	CNV	RS < 12 hours	Phenobarbital Lidocaine Midazolam
5/August 2004/F	25	820	9/10	90	Seizures	None	Blood	CNV	SS < 24 hours	Phenobarbital Lidocaine Midazolam Clonazepam
6/June 2006/M	32	2,225	9/10	53	Fever, irritability seizures, rash	None	CSF, nasopharynx	CNV	Clinical seizures only	None
7/August 2006/F	37	3,100	8/8	7	Irritability, seizures, apneas, diarrhea	Yes	CSF, blood	DNV	RS < 24 hours	Phenobarbital Lidocaine Midazolam
8/October 2006/M	39	2,680	8/9	7	Fever, irritability, seizures, apnea	Yes	Blood	CNV	SS < 12 hours	Phenobarbital
9/December 2006/F	39	3,230	NA	9	Lethargy, seizures, apnea	None	CSF	CNV	RS > 24 hours	Phenobarbital Phenytoin
10/September 2007/F	39	4,380	9/9	8	Fever, irritability, rash	None	CSF	NA	No seizures	None

[a]Dopamine was given at a maximum dose of 10μg/kg/min.
[b]This patient has been described previously as having enterovirus (EV) encephalitis (untypable EV strain has been cultured from the nasopharynx).
HPeV = human parechovirus; GA = gestational age; BG = background; aEEG = amplitude-integrated electroencephalograph; CSF = cerebrospinal fluid; DNV = discontinuous normal voltage; CNV = continuous normal voltage; RS = repetitive seizures; SS = single seizures; NA = not available.

The child with cerebral palsy (gross motor classification scale V), epilepsy, and cerebral visual impairment (Patient 1) had extensive cystic leukomalacia seen on both cUS and MRI at 38 weeks postmenstrual age.[12] The child with learning disabilities requiring special education (Patient 2, see Fig 1) had extensive changes in the white matter, especially well visualized with DWI. The child with postneonatal epilepsy (Patient 5) was the only infant with extremely low birth weight. The child with distal hypertonia (Patient 7, see Fig 2) showed a delay in myelination of the posterior limb of the internal capsule on both MRIs, as well as high signal intensity on DWI in the descending corticospinal tracts. Five patients (Patients 3, 4, 6, 8, and 9) show normal development at 4 years, 2 years, 18 months, 18 months, and 15 months, respectively. The neurodevelopmental outcome of Patient 10, who was admitted in October 2007, is normal at the early age of 9 months.

Amplitude-Integrated Electroencephalographic Findings

All but one of the infants were continuously monitored with the amplitude-integrated EEG (see Table 1). Postneonatal epilepsy occurred in two infants so far (Patients 1 and 5). Two of the four infants with an adverse outcome had repetitive seizures on a discontinuous background. The other two had a continuous normal voltage background but therapy-resistant seizures. One infant (Patient 6) showed a continuous background without any discharges. He presented with clinical seizures in the local hospital before admission to the NICU.

Table 2. **Cranial Ultrasound, Neonatal Magnetic Resonance Imaging Results, and Outcomes of 10 Patients with Human Parechovirus Encephalitis**

Patient No./ Birth Date/ Sex	Cranial Ultrasound Findings at Onset of Symptoms of HPeV Infection	Day of MRI after Onset of Symptoms (PMA)	MRI	MRI-Diffusion-Weighted Imaging	Outcome
1/March 1998/F	Severe periventricular echogenicity (cysts first seen after 2 weeks)	14 days (38 weeks)	Extensive cystic leukomalacia, lack of myelination of the PLIC on IR (MRI at 2 years extensive WM loss, severe gliosis of the periventricular WM)	NA	Cerebral palsy, epilepsy, CVI at 6 years
2/July 2000/F	Severe periventricular echogenicity	5 days (41 weeks)	Diffuse excessive high SI in the periventricular WM on T2SE, normal myelination of the PLIC on IR (MRI at 7 years gliosis of the periventricular WM)	High SI in the periventricular WM and the corpus callosum	Learning disabilities at 7 years of age
3/February 2002/M	Severe periventricular echogenicity	11 days (40 weeks)	Diffuse excessive high SI in the WM, multiple punctate WM lesions on T2SE, normal myelination of the PLIC on IR, lactate present in the WM (proton-MRS)	High SI in the periventricular WM and the corpus callosum, small infarction in left cerebral peduncle	Normal at 4 years of age
4/June 2004/F	Severe periventricular echogenicity	6 days (42 weeks)	Mild increase in SI in the WM, punctate WM lesions on T2SE, normal myelination of the PLIC on IR	Mild increase in SI in the periventricular WM and the corpus callosum and optic radiation	Normal at 2 years of age
5/August 2004/F	Severe periventricular echogenicity	3 days (38 weeks)	Mild increase in SI in the WM on T2SE, normal myelin of the PLIC on IR	High SI in the periventricular WM and the corpus callosum	Normal cognitive outcome at 3 years of age, epilepsy
6/June 2006/ M	Severe periventricular echogenicity	NA	MRI-NA, CT scan normal	NA	Normal at 18 months of age
7/August 2006/F	Severe periventricular echogenicity	6 days (38 weeks)	Diffuse excessive high SI in the periventricular WM with multiple punctate lesions on T2SE, delay in myelinization of PLIC on IR MRI at 3 months of age (delayed myelination of PLIC, early gliosis of periventricular WM)	High SI in the periventricular WM, the corpus callosum, optic radiation, internal capsule, and cerebral peduncle	Suspect at 18 months of age, mild distal hypertonia
8/October 2006/M	Severe periventricular echogenicity	6 days (39 weeks)	Excessive high SI in the periventricular WM on T2SE, normal myelination of PLIC on IR	High SI in the periventricular WM, the corpus callosum, and internal capsule especially on the right side	Normal at 18 months of age
9/December 2006/F	NA	1 day (40 weeks)	Multiple punctate areas of T1 hyperintensity and T2 hypointensity in deep WM, normal myelination of the PLIC on IR	Restricted diffusion in periventricular WM, deep WM, corpus callosum, internal capsule, posterior thalami, optic radiations, cerebral peduncles	Normal at 15 months of age
10/September 2007/F	Severe periventricular echogenicity	8 days (40 weeks)	Diffuse excessive high SI in the WM, multiple punctate WM lesions on T2SE, normal myelination of the PLIC on IR	High SI in the periventricular WM and the corpus callosum	Normal at 9 months of age

HPeV = human parechovirus; MRI = magnetic resonance imaging; PMA = postmenstrual age; PLIC = posterior limb of the internal capsule; IR = inversion recovery; WM = white matter; NA = not available; CVI = cerebral visual impairment; SI = signal intensity; T2SE = T2 spin-echo sequence; MRS = magnetic resonance spectroscopy; CT = computed tomography.

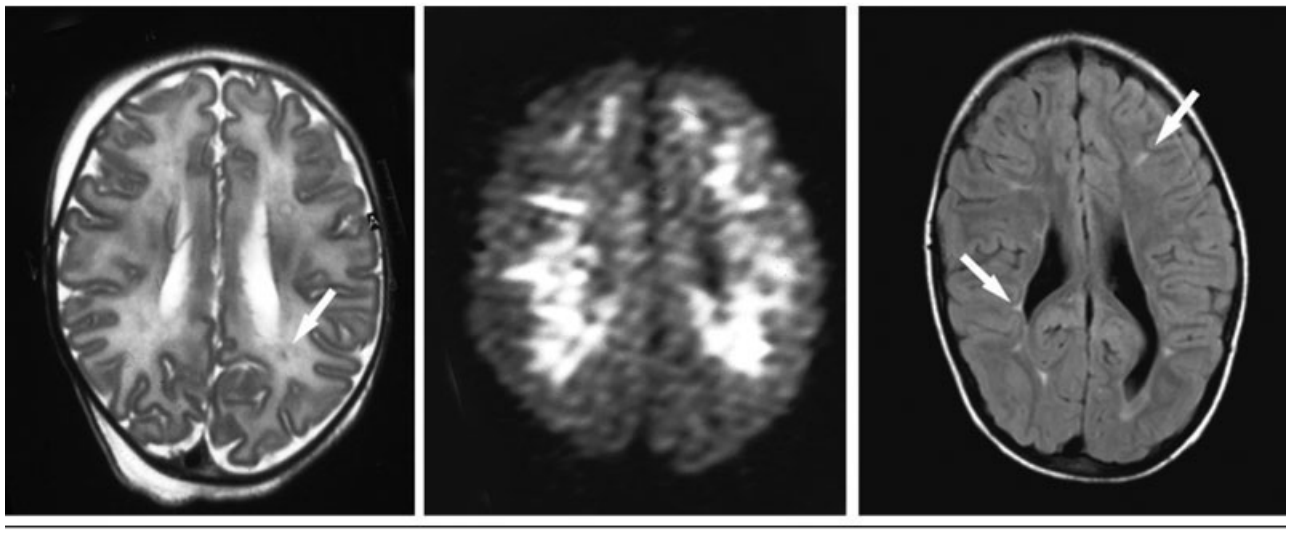

Fig 1. Magnetic resonance imaging (MRI) T2-weighted spin-echo sequences (left) and diffusion-weighted imaging (middle) 5 days after the onset of human parechovirus (HPeV) infection and fluid-attenuated inversion recovery sequence (right) at 7 years of age (Patient 2). Note diffuse increase in high signal intensity in the white matter mixed with several low signal intensity punctate lesions (arrow) *(left), diffuse high signal intensity in the periventricular white matter on diffusion-weighted imaging (DWI) (middle), and mild ventricular dilatation and punctate periventricular gliosis in the periventricular white matter* (arrows) *(right).*

Virology

The site of isolation of HPeV RNA is given in Table 1. Molecular typing of HPeV could be performed in eight infants, and HPeV type 3 was always identified.[4,5] Viral loads were too low for molecular typing in the remaining two patients. EV and herpes simplex virus cerebral infection were excluded in all infants.

Discussion

This is the largest group of infants with HPeV encephalitis reported to date, and the first time that associated extensive white matter involvement is shown in a group of neonates, using cUS and MRI. Clinical presentation was shown to be similar to EV encephalitis, but HPeV appears to be more common than EV encephalitis.[1] Newborn infants with EV or HPeV encephalitis present with fever, irritability, seizures, and frequently a rash. Cerebral infection with HPeV resulted in pleocytosis in only 1 of our 10 patients, and the protein and glucose levels were always normal. Absence of cell reaction in the CSF in HPeV infection has

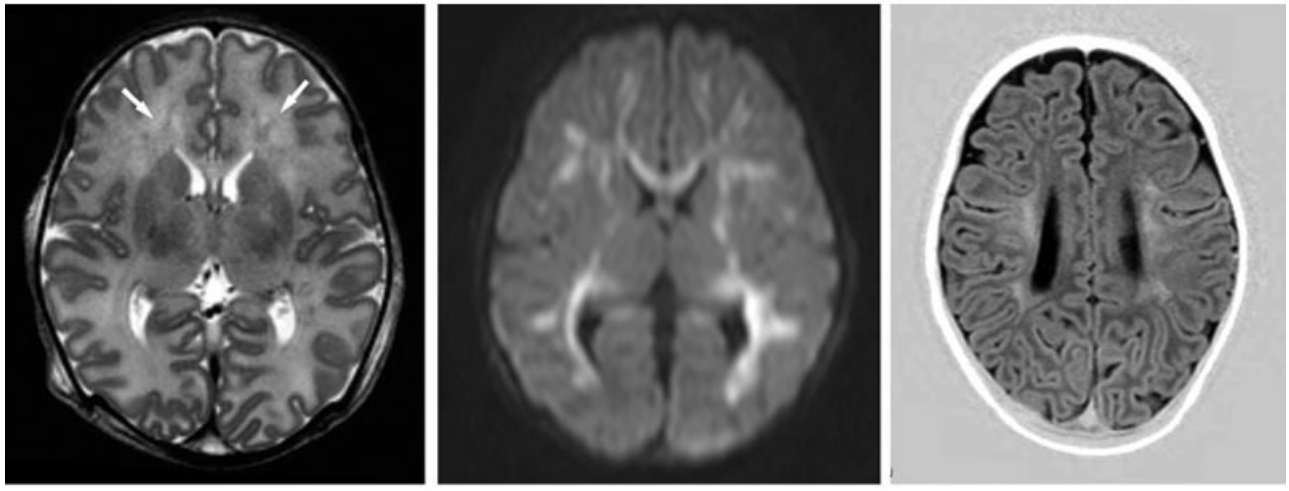

Fig 2. Magnetic resonance imaging (MRI) T2-weighted spin-echo sequence (left), diffusion-weighted imaging (middle) 6 days after the onset of human parechovirus (HPeV) infection, and inversion recovery sequence (right) at 3 months of age (Patient 7). Note multiple punctate white matter lesions (arrows) *(left) and diffuse excessive high signal intensity in the periventricular white matter, involving the optic radiation and the internal capsule (middle), and periventricular high signal intensity changes suggestive of early gliosis in the periventricular white matter at 3 months of age (right).*

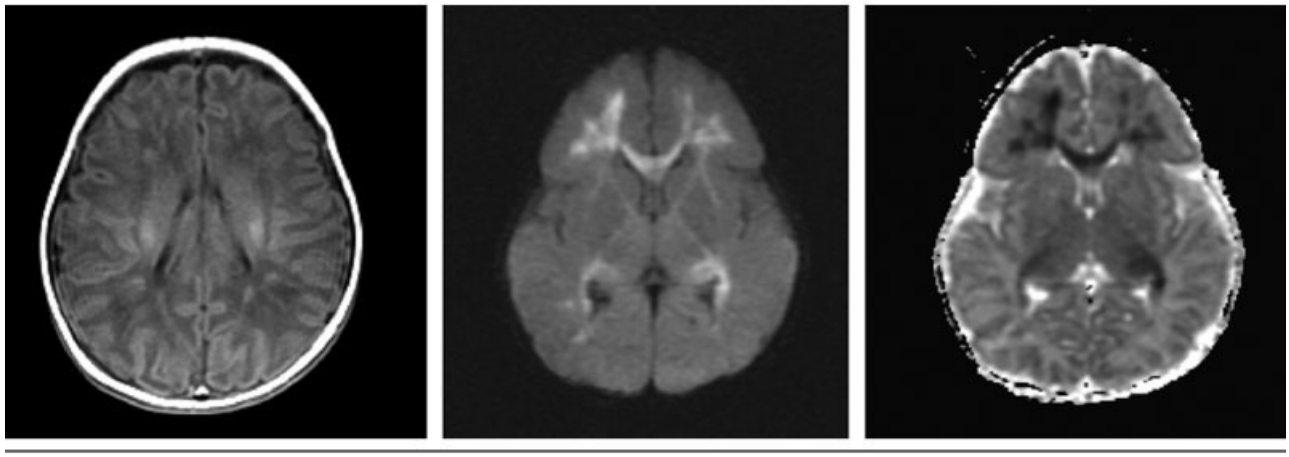

Fig 3. Magnetic resonance images (MRIs) obtained 1 day after the onset of human parechovirus (HPeV) infection (Patient 9). Note multifocal punctate areas of high T1 signal (left) and in deep white matter (WM). Diffusion-weighted imaging (middle) and apparent diffusion coefficient (ADC) map (right) demonstrate extensive areas of restricted diffusion in the periventricular WM, deep WM, corpus callosum, internal capsule, posterior thalami, optic radiations, and cerebral peduncles.

not been previously described. However, this phenomenon is known from infants with EV infection.[1]

So far, parechoviruses have not been reported as a common cause of severe neonatal disease. HPeV 1 and HPeV 2, previously known as echoviruses 22 and 23, are well known for their ability to cause mild respiratory and gastrointestinal disease.[2] Severe cerebral infection caused by HPeV 1 has been sporadically reported in adults and older infants.[13–15] The recently identified HPeV 3 has been isolated from infants with sepsis-like disease with cerebral symptoms,[4,5,11] and HPeV 4 was so far isolated from an infant with fever only.[8] Except for one report of disseminated HPeV1 (echovirus 22) infection in a 5-month-old infant that led to severe cerebral damage seen on cerebral computed tomographic scan and MRI of one of our neonates with encephalitis shown as an example in a review on neonatal cerebral infection, no cranial imaging data have so far been reported.[13,16]

We found mild-to-severe white matter abnormalities in our patients with HPeV meningoencephalitis. Diffuse signal intensity changes of the white matter and punctate white matter lesions, suggestive of petechial hemorrhages, were seen on T1- and T2-weighted spin-echo sequences. Increased signal intensity in the corpus callosum, optic radiation, internal capsule, and cerebral peduncle could be seen on DWI. Because these white matter lesions were better detected on DWI, DWI and

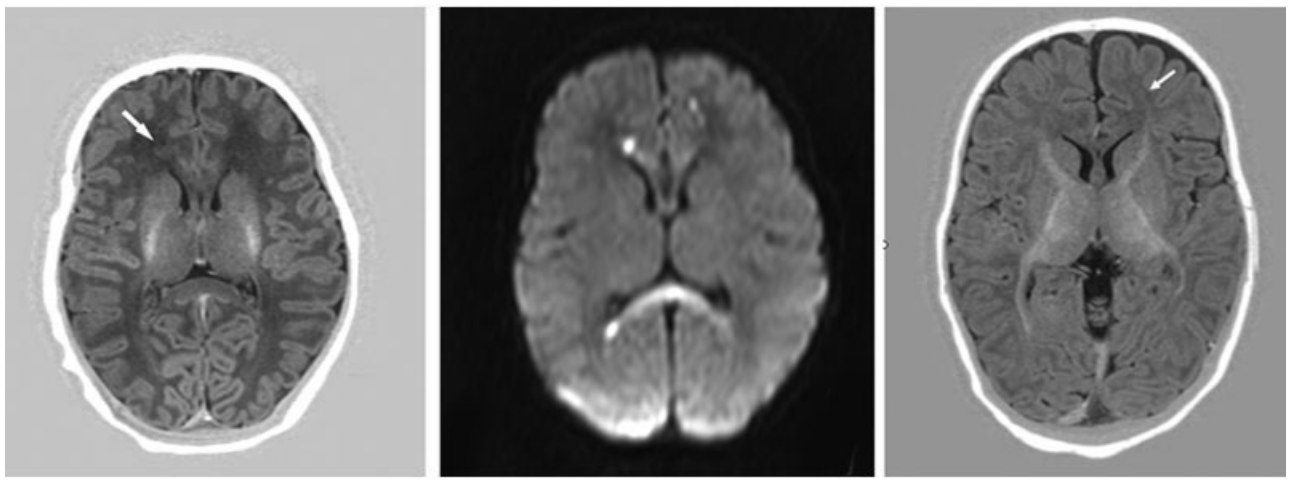

Fig 4. Magnetic resonance imaging (MRI) inversion recovery sequence (left) and diffusion-weighted imaging (middle) 6 days after the onset of human parechovirus (HPeV) infection (Patient 10). Note single high signal intensity punctate white matter lesion adjacent to the right frontal horn (arrow) *(left) and multiple punctate white matter lesions, as well as increased signal intensity in the corpus callosum on diffusion-weighted imaging in this infant who did not present with clinical seizures. (middle) MRI at 3 months shows residual white matter abnormalities* (arrow) *(right).*

apparent diffusion coefficient measurements provide additional information compared with other sequences in diagnosing white matter damage in the acute phase and should be performed in neonates suspected of a severe HPeV infection. Extensive white matter abnormalities were even seen in one patient who did not experience clinical seizures, suggesting that white matter abnormalities may be more common and may remain undetected, depending on the threshold of performing an MRI. The severity of the imaging abnormalities correlated with later neurodevelopmental outcome. The only child who experienced development of disabling cerebral palsy had extensive cysts in the white matter. The child with distal hypertonia showed involvement of the descending corticospinal tracts on early diffusion imaging. The child with poor school performance also had extensive early DWI changes followed by periventricular gliotic changes on a repeat MRI at 7 years of age. The extent of the diffusion changes that were present often suggested a more adverse motor outcome than was seen, based on experience in full-term infants with hypoxic-ischemic encephalopathy.[17] The localization of the lesions on cUS and MRI was similar to the abnormalities previously reported in infants with EV meningoencephalitis.[1]

Only 5 of our 10 patients show normal early neurodevelopment at ages 15 months to 7 years. The neurodevelopmental outcome of one patient admitted in 2007 is normal at the early age of 9 months.

A discontinuous background and repetitive seizures on amplitude-integrated EEG also correlated with poor neurodevelopmental outcome. Two of the four infants with a poor outcome had a continuous background but experienced development of therapy-resistant seizures.

The pathophysiology of viral infection of the CNS is not well understood. Recent data suggest that proinflammatory cytokines may be secreted by different CNS cell types including microglia, astrocytes, and neurons followed by infiltration of white blood cells. Termination of the inflammatory process occurs by production of antiinflammatory cytokines by activated T cells and/or monocytes after elimination of the virus.[18] In the immature brain, cytokines and perivascularly accumulated lymphocytes may lead to white matter damage.[19] Increased susceptibility of the neonatal CNS to EV in newborn mice has been presented previously.[20,21] Recent data using a mouse model showed that EV (coxsackievirus B3) could infect neuronal progenitor cells in the subventricular zone. EV was carried into the brain parenchyma by developing neurons that continued to migrate and differentiate despite the infection. Infected cells have lost their proliferative capacity, but despite being proliferation deficient, they could migrate along the rostral migratory stream and radial glia, to reach their final destinations in the olfactory bulb or cerebral cortex. On full maturation, infected neurons underwent apoptosis that resulted in neuronal loss.[22,23]

It is not possible to differentiate clinically neonatal seizures caused by HPeV from seizures caused by EV infection, which we described previously.[1] Furthermore, both infections predominantly occur in the summer and fall, with only sporadic infections in the winter months.[11,24,25]

The diagnosis of HPeV infection can be made only from a positive HPeV PCR in clinical samples, especially CSF, blood, or both. HPeVs can not be identified by the usual EV PCR because of the genetic differences between the EVs and HPeVs.

Because the clinical differentiation between EV and HPeV infection is difficult, both an EV RT-PCR and a HPeV RT-PCR on blood and CSF of patients presenting with neonatal seizures suggestive of viral origin should be performed to make the correct diagnosis. The diagnosis was made retrospectively in stored CSF in six infants, showing the importance of storing CSF in infants in whom a diagnosis could not be made.

We were able to type HPeV in 8 of our 10 infants. HPeV type 3 was identified in all of them. In contrast with HPeV types 1 and 2, previously known as echoviruses 22 and 23, the serotype 3 may cause severe neonatal disease, including encephalitis. This supports the results of two previous reports describing neonatal sepsis-like illness with cerebral manifestations caused by HPeV type 3.[4,5]

Conclusion

HPeV should be added to the list of neurotropic viruses that can lead to severe encephalitis associated with white matter injury in the neonatal period. White matter injury can be visualized with cUS, but more detailed information will be obtained with DWI-MRI. Because the clinical presentation is similar for EV and HPeV infection, both viruses should be investigated in atypical presentation of neonatal seizures.

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