Parechovirus Encephalitis and Neurodevelopmental Outcomes

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abstract

OBJECTIVE: We aimed to describe the clinical features and outcome of human parechovirus (HPeV) encephalitis cases identified by the Australian Childhood Encephalitis (ACE) study.

METHODS: Infants with suspected encephalitis were prospectively identified in 5 hospitals through the (ACE) study. Cases of confirmed HPeV infection had comprehensive demographic, clinical, laboratory, imaging, and outcome at discharge data reviewed by an expert panel and were categorized by using predetermined case definitions. Twelve months after discharge, neurodevelopment was assessed by using the Ages and Stages Questionnaire (ASQ).

RESULTS: We identified thirteen cases of suspected encephalitis with HPeV infection between May 2013 and December 2014. Nine infants had confirmed encephalitis; median age was 13 days, including a twin pair. All had HPeV detected in cerebrospinal fluid with absent pleocytosis. Most were girls (7), admitted to ICU (8), and had seizures (8). Many were born preterm (5). Seven patients had white matter diffusion restriction on MRI; 3 with normal cranial ultrasounds. At discharge, 3 of 9 were assessed to have sequelae; however, at 12 months' follow-up, by using the ASQ, 5 of 8 infants showed neurodevelopmental sequelae: 3 severe (2 cerebral palsy, 1 central visual impairment). A further 2 showed concern in gross motor development.

CONCLUSIONS: Children with HPeV encephalitis were predominantly young, female infants with seizures and diffusion restriction on MRI. Cranial ultrasound is inadequately sensitive. HPeV encephalitis is associated with neurodevelopmental sequelae despite reassuring short-term outcomes. Given the absent cerebrospinal fluid pleocytosis and need for specific testing, HPeV could be missed as a cause of neonatal encephalopathy and subsequent cerebral palsy.

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WHAT'S KNOWN ON THIS SUBJECT: Human parechoviruses (HPeV) are an increasingly recognized cause of meningo-encephalitis in young children, potentially associated with adverse neurodevelopmental outcomes. HPeV genotype 3 central nervous system infection is associated with young age (<3 months) and absence of cerebrospinal fluid pleocytosis.

WHAT THIS STUDY ADDS: Young age and prematurity appear to be risk factors for encephalitis in HPeV CNS infection. In HPeV encephalitis, cranial ultrasound is insensitive and a high proportion of infants experience neurodevelopmental sequelae. Outcome appears to correspond with severity of MRI changes.

To cite: Britton PN, Dale RC, Nissen MD, et al. Parechovirus Encephalitis and Neurodevelopmental Outcomes. *Pediatrics.* 2016;137(2):e20152848

Human parechoviruses (HPeV) are an increasingly recognized cause of meningo-encephalitis in children.[1–8] HPeV genotype 3 (HPeV3) is thought to be particularly neurotropic, being frequently identified from the cerebrospinal fluid (CSF) of infants with sepsislike presentations.[2,8–14] HPeV3 central nervous system (CNS) infection is associated with young age (<3 months) and absence of CSF pleocytosis.[2,4,6,9,11–20]

Most reports of HPeV infection of the CNS have been retrospective series identified through sampling of archived laboratory specimens, without application of clinical case definitions for encephalitis.[2,5,6,9–25] As a result, the syndrome of CNS infection with HPeV is inadequately characterized. Further definition of HPeV CNS syndromes are needed because although many infants have benign outcome after CNS infection,[4,8,13,16] there have been isolated reports of adverse neurodevelopmental outcomes with HPeV3 in the context of abnormal neuroimaging.[3,26,27]

Encephalitis is the most severe manifestation of HPeV CNS infection and rigorous case definitions for encephalitis have been published in the past 10 years in studies from California,[28] the United Kingdom,[29] and France,[30] as well as consensus definitions from the Brighton Collaboration[31] and the International Encephalitis Consortium.[32] The Australian Childhood Encephalitis (ACE) study is an ongoing prospective study of childhood encephalitis that uses these case definitions.

Herein, we report children who presented with suspected encephalitis who had laboratory-confirmed HPeV infection. We describe the key clinical features of this disease and its outcome at discharge and 12 months follow-up to better define severe CNS HPeV infection.

METHODS

Children (≤14 years of age) hospitalized with "suspected encephalitis" were prospectively identified and recruited to the ACE study at 5 Australian tertiary pediatric hospitals in the Australian Pediatric Active Enhanced Disease Surveillance network (PAEDS[33]; www.paeds.edu.au) between May 2013 and November 2014: Children's Hospital at Westmead, Sydney, New South Wales (NSW) from May 2013; the Royal Children's Hospital, Brisbane, Queensland, from February 2014; and the Royal Children's Hospital, Melbourne, Victoria, Women's and Children's Hospital, Adelaide, South Australia, and Princess Margaret Hospital, Perth, Western Australia, all from April 2014. Comprehensive demographic details, clinical features, vaccination history, results of medical imaging and laboratory tests, immunization history, and details of treatment and outcome at discharge were collected. The ACE study is observational and the investigation and management of cases is determined by treating physicians. We confirmed cases to be HPeV-related following review by a cross-disciplinary expert panel (pediatric infectious diseases, microbiology, neurology, and epidemiology) who also categorized cases as confirmed encephalitis or "not encephalitis" by using the International Encephalitis Consortium definition and Brighton criteria.[31,32]

Parechovirus molecular testing was performed by using in-house assays: NSW and Victorian cases at the Victorian Infectious Diseases Reference Laboratory, as previously described[34,35]; Queensland cases at Royal Children's Hospital, Brisbane, according to the protocol described by Benschop et al.[36]

Suspected encephalitis was defined as encephalopathy (altered level of consciousness, lethargy, or behavior and/or personality change) lasting ≥24 hours with ≥1 of the following: fever, seizures, focal neurologic findings, at least 1 abnormality of CSF (age determined pleocytosis, or elevated protein ≥40 mg/dL), or EEG/neuroimaging findings consistent with encephalitis.

Short-term outcome at discharge was measured by using the Glasgow outcome scale (GOS) assigned by the PAEDS nurses and investigators at each site in consultation with the attending clinicians.[37] Outcome at 12 months after discharge was measured by using the age-appropriate Ages and Stages questionnaire version 3 (ASQ-3; http://agesandstages.com/) sent to the parents, and then reviewed with one of the investigators in a telephone interview. The questionnaire responses were categorized as "significant," "some," or "no" developmental concern identified according to ASQ-defined subscale cutoff scores (quantitative results: significant concern corresponds to the ASQ cutoff set at <2 SD below the population mean; some concern corresponds to the cutoff set at <1 SD and ≥2 SD). Where concern was identified in the overall responses section of the ASQ (qualitative results), the response was categorized as some concern.

Ethics approval for the ACE study including long-term follow-up (with caregiver consent) was obtained from all 5 study sites. Data were analyzed descriptively by using Microsoft Excel, 2010 (Microsoft, Redmond, WA).

RESULTS

We identified 13 infants with suspected encephalitis and HPeV infection from a total of 133 suspected encephalitis cases from all causes identified through the ACE study between May 2013 and November 2014 (Table 1). Following expert panel review, 9 of the 13 infants were categorized

as encephalitis and 4 as "not encephalitis."

Of the 9 infants fulfilling encephalitis criteria (see Table 1), 7 were girls, and 5 were born prematurely (28–35 weeks' gestation). All occurred in infants ages <2 months, with a median age of 13 days (uncorrected; corrected for gestational age at birth, 9 days). Two of the infants (cases 8, 9) were monochorionic twins who were unwell at the same time. In 2 patients (cases 6, 11), an unwell older sibling was identified as a sick contact; a parent was not reported to be concurrently unwell in any case. All infants were outpatients who presented with an acute onset of fever, lethargy, and irritability. Lethargy or decreased arousability was the defining feature of encephalopathy identified in these infants. Additional features of encephalopathy included decreased/inconsistent response to external stimuli (n = 6; 67%) and disinterest in feeding (n = 5; 56%). A seizure occurred in 8 of the 9 children (89%), associated in 5 with loss of consciousness: a critical feature in confidently categorizing cases. In 3 cases, the initial seizure was not associated with fever. Rash was present in 5 (56%; frequently diffuse erythema or maculopapular involving the trunk). Four of the children had clinical and/or laboratory evidence of multiorgan dysfunction (44%; see Table 1). Although HPeV RNA was identified in the CSF of all 9 cases, CSF pleocytosis was lacking in all (see Table 1): median CSF white cell count 1 (WCC; range: 0–6 × 10^6/L), median CSF protein 0.71 (range: 0.39–0.8 g/L). HPeV subtyping was performed in 4 of 8 patients from NSW; all were genotype 3; subtyping was not performed on patients outside NSW.

Neuroimaging included cranial ultrasound in 7 children (2 abnormal; 29%) and MRI in 7 (all abnormal; see Tables 1 and 2). The key features on MRI were T2 hyperintensity and corresponding diffusion restriction (n = 7; 100%) involving the periventricular and subcortical white matter (WM) (n = 6; 86%), corpus callosum (n = 3; 43%), and thalami (n = 4; 57%) (Table 2); these findings were most often symmetrical (Fig 1). In 3 children, magnetic resonance spectroscopy (MRS) was also performed and showed decreased N-acetylaspartate (NAA), increased choline, and a lactate peak in 2 of 3: findings that infer the presence of demyelination, axonal injury, and possible necrosis in affected areas. In the 5 children in whom both tests (ie, cranial ultrasound and MRI) were performed, the cranial ultrasound was normal in 3. EEG was performed on 7 children, and was abnormal in 6 (85%; in 1 infant [case 1] with an EEG reported to be normal, epileptic discharges were shown on continuous EEG monitoring).

Eight (89%) infants required an ICU admission; 5 (56%) received invasive mechanical ventilation, 1 (11%) continuous positive airway pressure support, and 3 (33%) inotrope infusions. The median length of stay in ICU was 6 days (range: 4–13 days): in hospital, 11 days (range: 4–13 days). All of the infants received intravenous antibiotics for between 2 and 8 days; 7 of 9 infants received empirical acyclovir for between 2 and 5 days; 4 of the 9 (cases 1, 2, 6, 9) received corticosteroids. In 2 cases, corticosteroids were given in addition to inotropes for hypotension, were given in another case for possible "inflammatory" encephalitis, and in 1 case the rationale was not given.

Short-term outcome indicated none, or minor neurologic sequelae (GOS 5) for 6 of the 9 (67%) cases, the remaining 3 (33%) having moderate neurologic sequelae (GOS 4). The ASQ-3 was completed in 8 of 9 children at ∼12 months after discharge, when they were aged between 13 and 15 months (see Table 2). In 5 (63%) of the 8, "significant" developmental concern was identified. In 2 children (cases 8 and 9; twin girls), a diagnosis of cerebral palsy had been made; in 1 child (case 5), a diagnosis of central visual impairment had been made. In the other 2 children, ASQ scores fell below cutoffs in 1 or more domains (see Table 2); notably, in all 5, scores fell below the cutoff in the gross motor subscale. Additionally, in the 2 (25%) children in whom "some" concern was identified, this was in the gross motor subscale. The severity of outcome appeared to correspond with the severity of MRI changes (extent of distribution, presence of necrosis; see Table 2 and Fig 1).

Of the 4 children infected with HPeV who were not categorized as encephalitis, 2 were definitively categorized as "not encephalitis" (cases 12, 13) because of a lack of clinical features of encephalopathy. Two cases (cases 10 and 11) appeared to have encephalopathy (decreased arousability) but could not be definitively categorized in the absence of neuroimaging and/or EEG data. These 4 children were slightly older (3/4 >26 days; median age 60.5 days). Their clinical features overlapped with the encephalitis cases (Table 1), although none had seizures or were born preterm. Short-term outcome indicated none, or minor sequelae (GOS 5) for all nonencephalitis cases. Twelve-month follow-up was completed with 3 of 4 children. In 2 of 3 (67%), no developmental concern was identified. In 1 (case 13), "some" concern was qualitatively identified, with regard to behavior: also quantitatively evident in the personal-social subscale.

DISCUSSION

We have presented a series of 13 consecutive infants with confirmed HPeV infection who were prospectively identified with suspected encephalitis through

TABLE 1 Demographics, Clinical Features, and Diagnosis of Infants With HPeV Infection Recruited to the ACE Study

Case	Month of Admission	Age, d (corrected[a])	Gender	Clinical Features: Encephalitis Criteria (Noncriteria)	Comorbid: Birth Gestation (wk)	Neuroimaging	CSF Findings	EEG	Hospitalization: ICU; Total LOS
Encephalitis									
1	November 2013	9	M	Lethargy, seizures, fever (irritability, poor feeding, rash, "septic")	Nil	cU/S normal, MRI abnormal	WCC 1, RBC 0, Prot 0.39 PeV PCR pos[b,c] (genotype 3)	Abnormal	NICU; 13 d
2	November 2013	12 (–2)	F	Lethargy, fever (irritability, rash, diarrhea, poor feeding, "septic")	Ex-prem (35), Ocular dysplasia	cU/S normal, MRI abnormal	WCC 0, Prot 0.72 PeV PCR pos[b,c] (genotype 3)	Not done	PICU; 12 d
3	December 2013	53	F	Lethargy, seizures, fever (irritability, poor feed, "septic," tachycardia, abdominal distension)	Nil	cU/S normal	WCC 21 (18 PMN), RBC 29500[d] Prot 0.64 PeV PCR pos	Normal	Nil ICU; 5 d
4	December 2013	8	F	Lethargy, seizure, fever (poor feeding, rash)	Nil	cU/S nonspecific	WCC 0, Prot 0.77 PeV PCR pos	Abnormal	NICU; 4 d
5	December 2013	60 (6)	F	Lethargy, seizures, decreased LOC, weakness (irritability, cytopenias, coagulopathy, abdominal distension)	Ex-prem (28)	MRI abnormal	WCC 1, Prot 0.63 PeV PCR pos	Abnormal	PICU; 12 d
6	March 2014	13 (–1)	M	Lethargy, decreased LOC, seizures (irritability, rash)	Ex-prem (35)	cU/S normal, MRI abnormal	WCC 1, Prot 0.72 PeV PCR pos	Abnormal	PICU; 7 d
7	April 2014	10	F	Lethargy, seizures, fever (irritability, poor feeding, rash)	Nil	MRI abnormal	WCC 5, Prot 0.71 PeV PCR pos	Abnormal	PICU; 10 d
8 Twin 1	June 2014	32 (11)	F	Lethargy, seizures, fever (irritability, poor feed, vomiting, hepatitis, coagulopathy)	Ex-prem (34)	cU/S abnormal, MRI abnormal	WCC 0, Prot 0.51 PeV PCR pos	Abnormal	NICU; 11 d
9 Twin 2	June 2014	33 (12)	F	Lethargy, seizures, fever (irritability, poor feed, vomiting, hepatitis, coagulopathy, "septic")	Ex-prem (34)	cU/S abnormal, MRI abnormal	WCC 6, Prot 0.8 PeV PCR pos	Not done	NICU; 12 d
Not definitively categorized									
10	November 2013	8	F	Lethargy, fever, (irritability, rash, hepatitis, cytopenias)	Nil	cU/S normal	WCC 4, RBC 310, Prot 0.66 PeV PCR pos (genotype 3)	Not done	NICU; 6 d
11	October 2013	86	F	Lethargy, fever (irritability, rash, tachycardia)	Nil	cU/S normal, CT normal	WCC 57 (20 PMN), RBC 132000,[d] Prot 8.2 PeV PCR pos[b]	Not done	Nil ICU; 8 d
Not encephalitis									
12	November 2013	26	F	Fever (irritability, rash)	Nil	MRI "nonspecific"	WCC 2, RBC 1850, Prot 0.41 PeV PCR pos (genotype 3)	Not done	Nil ICU; 6 d
13	December 2013	69	M	Fever (irritability, poor feeding)	Nil	Nil	WCC 8, RBC 0, Prot 0.24 PeV PCR neg[b]	Not done	Nil ICU; 4 d

cU/S, cranial ultrasound; CT, computed tomography; ex-prem, born at premature gestation; F, female; LOC, level of consciousness; LOS, length of stay; M, male; PeV, parechovirus; PMN, poly-morpho-nuclear cell; Prot, protein (g/L); RBC, red blood cell.

[a] Corrected to 37-weeks' gestation as term.

[b] Parechovirus PCR also positive in stool.

[c] Norovirus PCR positive in stool.

[d] These CSF WCC considered normal when corrected for RBC in CSF and PMN: total WCC proportions compared in CSF and blood. Adjusted CSF WCC 0 for both cases.

TABLE 2 Neuroimaging, EEG features, and Outcome of Infants With Parechovirus Encephalitis Recruited to the ACE Study

Case	Neuroimaging (Day of Illness)	EEG	Discharge Outcome: GOS	12-mo Outcome: ASQ
1	Cranial ultrasound (d2): normal.	Abnormal: Formal normal; subclinical epileptic discharges on continuous EEG monitoring.	5; nil/minor sequelae	Significant concern:
	MRI (d15): Appearance: Subtle T2 hyperintense, diffusion restriction. Distribution: Splenium corpus callosum and right occipital WM.			Quantitative: gross motor subscale. Qualitative: uses legs "less well" than arms.
2	Cranial ultrasound (d6): normal. MRI (d8): Appearance: T2 hyperintense, diffusion restriction. Distribution: Bilateral periventricular WM and genu corpus callosum.	Not done.	5; nil/minor sequelae	Some concern: Qualitative: favors right arm; walks on toes.
3	Cranial ultrasound (d2): normal.	Not done.	5; nil/minor sequelae	No concern.
4	Cranial U/S (d4): Cystic changes in the caudothalamic groove bilaterally.	Abnormal: frequent sharp activity over vertex and right temporal region.	5; nil/minor sequelae	Some concern: Qualitative: not yet walking; sister was walking at same age.
5	MRI (d3): Appearance: T2 hyperintense, diffusion restriction.	Abnormal: diffuse attenuation of background; most marked over the left hemisphere where brief, subclinical epileptic discharges seen.	4; moderate sequelae	Significant concern:
	Distribution: Most supratentorial WM and parieto-occipital cortex + precentral gyrus of frontal lobe; bilateral thalami. MRS: decreased NAA, increased choline, no definite lactate peak.			Quantitative: communication, gross motor, fine motor, problem-solving and personal-social subscales. Qualitative: "frustrated easily." Diagnosed with central visual impairment.
6	Cranial ultrasound (d2): normal.	Abnormal: epileptic discharges from both hemispheres, most subclinical, several arising from right temporal region.	4; moderate sequelae	Nil follow-up achieved.
	MRI (d3): Appearance: T2 hyperintense, diffusion restriction. Distribution: Most supratentorial WM (periventricular, deep + subcortical + corpus callosum), parieto-occipital cortex + precentral gyrus of frontal lobe; bilateral thalami show evidence of hemorrhage (T2 hypointense, T1 hyperintense). MRS: decreased NAA, increased choline, lactate peak.			
7	MRI (d2): Appearance: T2 hyperintense, diffusion restriction.	Abnormal: background slowing and multifocal epileptiform discharges.	4; moderate sequelae	Significant concern:
	Distribution: Bilateral cerebral hemispheres, subcortical WM (especially frontal) and periventricular WM; small subarachnoid hemorrhage. MRS: widespread lactate peak.			Quantitative: gross motor and problem-solving subscales. "Some concern" on fine motor subscale. Qualitative: "frustrated easily," difficult to settle. Diagnosed with left ocular "squint," mild left-sided weakness.
8	Cranial ultrasound (d7): abnormal	Abnormal: multifocal epileptiform discharges.	5; nil/minor sequelae	Significant concern:

TABLE 2 Continued

Case	Neuroimaging (Day of Illness)	EEG	Discharge Outcome: GOS	12-mo Outcome: ASQ
	MRI (d11): Appearance: T2 hyperintense, diffusion restriction. Distribution: Bilateral, extensive periventricular WM, corpus callosum, and bilateral thalami.			Quantitative: gross motor and problem-solving subscales. "Some concern" on communication, fine motor, personal-social subscales. Qualitative: diagnosed with cerebral palsy, ocular "squint," "frustrated easily."
9	Cranial ultrasound (d3): abnormal. MRI (d10): Appearance: T2 hyperintense, diffusion restriction, areas of necrosis and hemorrhage. Distribution: Bilateral, extensive periventricular WM, corpus callosum, bilateral thalami, cerebellar peduncles, hippocampi.	Not done.	5; nil/minor sequelae	Significant concern: Quantitative: communication, gross motor, problem-solving, and personal-social subscales. "Some concern" on fine motor subscale. Qualitative: diagnosed with cerebral palsy, ocular "squint," "frustrated easily."

the ACE study, including 12-month neurodevelopmental follow-up by using a well-validated screening tool. HPeV accounted for 10% of total suspected encephalitis cases identified over the surveillance period, during which a large outbreak of HPeV3 infection occurred in Eastern Australia.[38] Nine infants had confirmed HPeV encephalitis. Most were girls and born preterm. Key features included generalized seizures, lethargy (decreased arousability), an absence of CSF pleocytosis, and subcortical WM changes on MRI. In addition, all HPeV encephalitis cases required intensive care support, emphasizing the severity of the disease. We have observed a high proportion with neurodevelopmental sequelae at 12 months follow-up. We acknowledge that we cannot draw definitive genotype-specific conclusions because HPeV genotyping was not performed on cases outside NSW. However, we think it is likely that all these cases are HPeV3 associated because they have a similar phenotype, they all occurred within a 6-month period, they are all from the east coast of Australia, and HPeV3 was identified among other specimens in state reference laboratories during the period.[34,39]

Our study confirms features described in a similarly sized, retrospective series reported by Verboon-Maciolek et al,[3,40] and shows that young age and premature birth are possible risk factors for encephalitis in HPeV infection, that female gender is overrepresented, and that cranial ultrasound is an inadequately sensitive imaging modality in this disease. We also show that, although short-term outcomes may be reassuring, a high proportion of infants experience neurodevelopmental sequelae.

A retrospective report of 118 children hospitalized with HPeV infection from the Eastern Australian outbreak also has been published.[34] In this report, most (75/118) cases had CNS infection confirmed by the presence of HPeV RNA on polymerase chain reaction (PCR); however, infants with mild CNS HPeV infection were not differentiated from those with more serious disease, due to the lack of application of formal clinical definitions of encephalitis. When compared with this retrospective series, our prospectively collected HPeV encephalitis cases were younger (median 13 days compared with median 39 days[34]) and more likely to be girls (7/9 compared with 53/118 [45%][34]). This, and the high proportion of prematurity in our series suggests that young age may be a risk factor for encephalitis from HPeV infection, and that there may be a gender difference in susceptibility. We note that a similar proportion of girls and ex-premature infants were reported, although not highlighted, by Verboon-Maciolek et al.[3] This female predominance among HPeV encephalitis cases is in contrast to a male predominance in studies of HPeV3 with "sepsislike" disease.[11,14,16,20,23] Other studies of HPeV3 CNS infection include relatively few, if any, clinician-diagnosed encephalitis cases.[6,8,11,14,16,20,22,26,27,41] Among these cases, young age and female gender were prominent (data not presented).The MRI findings of bilateral symmetrical WM abnormalities with diffusion restriction, where present, should encourage clinicians to consider testing for HPeV in cases of neonatal encephalitis/encephalopathy. Diffusion-weighted imaging (DWI) appears particularly sensitive and characteristic in HPeV encephalitis. Although Verboon-Maciolek et al emphasize the utility of cranial ultrasound in HPeV encephalitis, our series suggests that cranial ultrasound is insensitive, at least early in the disease course.[3] Cranial ultrasound should not be used as a screening or "rule-out" test in suspected encephalitis in neonates. The MRI changes in HPeV encephalitis are, however, not specific. Similar changes have been described in neonatal enterovirus

encephalitis,[42,43] where, interestingly, an absence of CSF pleocytosis often occurs.[16,40] Furthermore, these imaging findings are reminiscent of perinatal WM injury from other causes that are known to result in periventricular leukomalacia and a high risk of cerebral palsy.[44,45] The periventricular and subcortical WM is vulnerable in young children, especially premature infants, and similar patterns of cellular damage can be initiated by ischemia, inflammation, or both.[44,46] A considerable literature now supports the importance of inflammatory mechanisms as a cofactor in perinatal WM injury.[46,47] Of particular note is the cytokine-mediated direct stimulation of immune cells within the CNS producing cellular activation and tissue damage, in the absence of inflammatory cell migration across the blood brain barrier.[48,49] Additionally, in vitro studies show that HPeV3 has specific neuronal tropism.[50] This may explain how HPeV3 CNS infection can result in significant tissue damage, in the absence of CSF pleocytosis, and relatively low viral loads seen in CSF.[14,25] There are few cases of HPEV3 CNS infection with published histopathology to contribute to our understanding.[51,52] One case did show "inflammatory cell infiltrates in the CNS tissue"[51]; it is unclear in another.[52] Encephalitis, strictly speaking, is a pathologic entity of brain parenchyma inflammatory cell infiltration and we concur with the hypothesis of Volpe,[49] that this disease may involve pathogenic pathways other than parenchymal lymphocytic infiltration.

At the severe end of the HPeV disease spectrum, it appears that a high proportion of children suffer neurodevelopmental sequelae. In this series, 7 of 8 children showed neurodevelopmental sequelae or concern of abnormal neurodevelopment 12 months after discharge. Among those

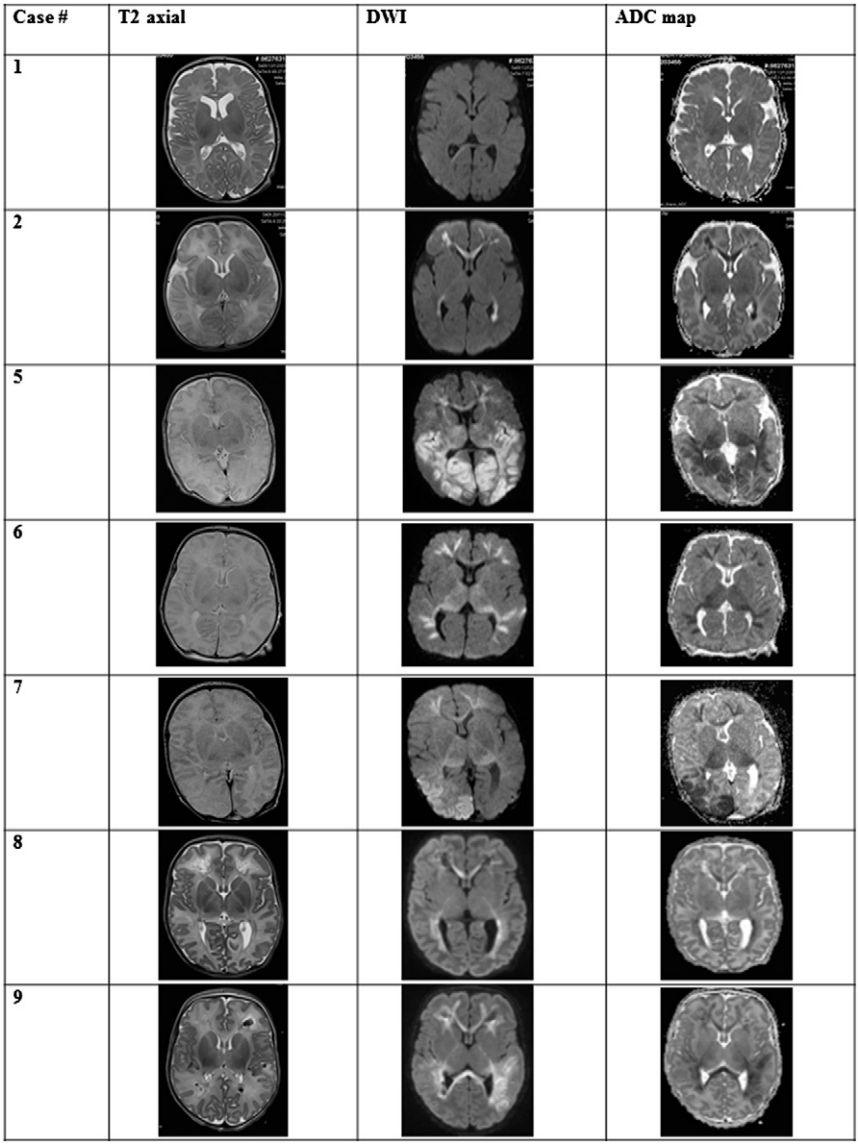

FIGURE 1

MRI in infants with parechovirus encephalitis. Case 1 shows subtle T2 hyperintensity in the right occipital periventricular WM with corresponding diffusion restriction. Additional diffusion restriction in the splenium of the corpus callosum and the anterior limb of the left internal capsule is seen on DWI/ADC map. Case 2 shows T2 high signal of the periventricular WM (frontal, parietal, and temporal) with corresponding diffusion restriction. Additional diffusion restriction in the genu of the corpus callosum is seen on DWI/ADC map. Case 5 shows extensive T2 high signal of cerebral WM, most pronounced posteriorly and involving the parieto-occipital cortex, and patchy high signal in the bilateral thalami with corresponding diffusion restriction. Case 6 shows symmetrical T2 high signal of periventricular and subcortical WM involving frontal and parieto-occipital cortex, and the dorsolateral thalami with corresponding diffusion restriction. Additional diffusion restriction in the genu of the corpus callosum is seen on DWI/ADC map. Not shown are small foci of T2 hypointensity in the frontal region with high signal that may represent foci of hemorrhage. Case 7 shows T2 high signal and loss of gray-white differentiation in the right occipital, temporal, and parietal lobes with some effacement of the occipital horn of the lateral ventricle. Extensive diffusion restriction is seen in the right occipital, temporal, and parietal cortex, and periventricular and subcortical WM is most marked in the frontal region. There is patchy diffusion restriction within the deep gray matter, most marked in the thalamic pulvinar bilaterally. Not shown is a small overlying extra-axial hemorrhage that appears subarachnoid. Case 8 shows extensive T2 (BLADE) high signal surrounding the ventricular poles with patchy cystic change in the frontal regions, and high signal within the thalamic pulvinar bilaterally and throughout the corpus callosum. Corresponding regions show diffusion restriction. Case 9 shows widespread and severe T2 (BLADE) high signal surrounding the ventricular poles with large areas of cystic necrosis and hemorrhage (T1 hyperintensity and shown

with "significant concern" on developmental screening, 2 have been diagnosed with cerebral palsy and all fall below the age-appropriate cutoffs in motor development. This is a striking finding and emphasizes the possible pathogenic overlap we have hypothesized with other causes of perinatal WM disease. Short-term outcomes, however, may be falsely reassuring. We would note that in cases of reportedly normal outcomes despite abnormal neuroimaging in the literature, follow-up has been short[4,26] when children are still young. Additionally, diffusion restriction on MRI has been shown to be an independent risk factor for adverse outcomes of childhood encephalitis generally.[53,54] Furthermore, neurologic deficits (especially subtle deficits) will manifest variably during this dynamic period of neurodevelopment in early childhood. There is a need for longer-term follow-up of the broad spectrum of HPeV CNS disease, stratified by genotype where it is known, to definitively determine the connection between HPeV CNS infection and long-term neurologic outcome. Until these studies are complete, given the MRI changes in the absence of CSF pleocytosis, and poor outcomes of some children, we suggest that a precautionary approach be taken in young children hospitalized with parechovirus infection. This includes a low threshold for HPeV PCR testing of CSF in febrile, irritable infants despite normal microscopy; applying the presumptive diagnosis "meningo-encephalitis" where HPeV RNA is found; performing optimal CNS imaging with MRI (where available); and providing neurodevelopmental follow-up until, at least, school entry to detect sequelae and facilitate early intervention where required.

An additional possible genetic predisposition to HPeV encephalitis is suggested by the presence of monochorionic twin girls in this series. Single gene defects have been associated with susceptibility to some causes of infectious encephalitis/encephalopathy in children.[55,56] There is a need to apply next-generation sequencing to identify genetic determinants of severe disease in well-described cohorts of children with CNS infection. This will provide new insights into disease pathogenesis.

There are currently no antiviral agents that can be used in HPeV treatment. Pleconaril, an agent broadly active against other picornaviruses with extremely limited availability, has minimal in vitro activity against HPeV.[57] Intravenous immunoglobulin is used widely in the treatment of enterovirus 71 neurologic disease without definitive evidence.[58] It also has been used without definitive evidence of effect in neonatal enteroviral encephalitis and myocarditis. Intravenous immunoglobulin may be of limited value for HPeV, depending on the prevalence of HPeV seropositivity in donor communities.[57] The role of corticosteroids remains unknown, although we note their use in this series of patients (4 of 9), albeit in 2 patients for hemodynamic support. Extended courses of antibiotics were given empirically to many of the infants presented in this series. This was influenced in some children by a delay in ordering specific HPeV testing and the time taken to receive results because testing was performed at referral laboratories. A greater awareness of HPeV disease in infants and greater availability of testing would likely result in earlier discontinuation of antibiotics.[25]

The lack of CSF pleocytosis in severe parechovirus CNS infection highlights the need for additional CSF markers of CNS inflammation in young children. Neopterin has been shown to be a useful marker of immune activation in CNS inflammatory and infectious conditions.[59] CSF neopterin was performed in only 1 child in our series (case 2) and was elevated (72 nmol/L; normal <30 nmol/L). Brownell et al[26] published a case of HPeV3 encephalitis in an 8-day-old boy with elevated CSF neopterin without other markers of CSF inflammation. Translation of neopterin as a biomarker of CNS inflammation into clinical settings is a priority, although the need for testing on fresh samples remains a diagnostic barrier.

The very young age of these children suggests acquisition of infection from a household contact; however, in only 2 of 13 cases was a sick household contact identified. Importantly, recent data from Japan have shown the potential role of asymptomatic household contacts, including siblings, as sources of infection.[60] An emphasis on hand hygiene in the home, especially during epidemics, is an important measure to prevent transmission of infection to young infants.

A challenge in studying childhood encephalitis is defining the specific features of encephalopathy in very young children. Irritability and poor feeding are frequently reported symptoms in HPeV, although we have chosen not to consider them as core features of encephalopathy in our study because they are

FIGURE 1 Continued

on susceptibility-weighted sequences, not shown) in the frontal and parietal lobes, and high signal within the thalamic pulvinar bilaterally and throughout the corpus callosum. Corresponding regions show diffusion restriction. ADC, apparent diffusion coefficient; BLADE, Siemens Healthcare (Australia/New Zealand Siemens Healthcare Headquarters Siemens Healthcare Pty Ltd, Bayswater, Victoria, Australia) proprietary name for periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER).

nonspecific features of illness in young infants. Given the typical lack of CSF pleocytosis and that some of these children (cases 10 and 11) did not have optimal CNS imaging nor were EEGs performed, one cannot aggregate the features of CNS inflammation to apply clinical case definitions of encephalitis. Others have noted this difficulty in defining the spectrum of HPeV CNS infection.[25]

The limitations of this series are primarily related to the observational nature of the ACE study and include the lack of HPeV genotyping on all cases and that not all suspected encephalitis cases identified by the ACE study have been tested for HPeV although awareness of this disease was high during the surveillance period; that the neuroimaging approach (MRI sequences, timing) was not standardized; and that we cannot contribute data/specimens to directly inform our understanding of disease pathogenesis.

CONCLUSIONS

We report a well-defined case series of HPeV encephalitis/encephalopathy, with the key clinical and neuroimaging features, and demonstrated a high proportion of cases with adverse neurodevelopmental outcome. We have identified unresolved questions with regard to pathogenesis and prognosis that are priorities for future research.

ACKNOWLEDGMENTS

We thank the full PAEDS-ACE investigator group: Prof Alison Kesson, Prof Helen Marshall, A/Prof Christopher Blyth, and Prof Julia Clark. We thank the PAEDS nurses: Jocelynne McRae, Helen Knight, Laura Rost, Sharon Tan, Sonia Dougherty, Donna Lee, and Alissa McMinn. We also thank Dr Kieran Frawley, Dr Umesh Shetty, and Dr Gillian Long, who were the reporting radiologists at Royal Children's Hospital, Brisbane, for cases 5, 6, and 7, respectively; and Dr John Fitzgerald, who was the reporting radiologist at Royal Children's Hospital, Melbourne, for cases 8 and 9.

ABBREVIATIONS

ACE: Australian Childhood Encephalitis
ASQ: Ages and Stages questionnaire
CNS: central nervous system
CSF: cerebrospinal fluid
DWI: diffusion-weighted imaging
GOS: Glasgow Outcome Scale
HPeV: human parechovirus
MRS: magnetic resonance spectroscopy
NAA: N-acetylaspartate
NSW: New South Wales
PAEDS: Paediatric Active Enhanced Disease Surveillance network
PCR: polymerase chain reaction
WCC: white cell count
WM: white matter

the study and reviewed and revised the manuscript; Dr Macartney was the lead PAEDS investigator at the Children's Hospital at Westmead (New South Wales), and reviewed and revised the manuscript; Dr Khandaker conceptualized the study and completed the 12-month follow-up of participants, and reviewed and revised the manuscript; Dr Booy conceptualized the study, drafted initial surveillance protocols, was part of the study expert panel, and reviewed and revised the manuscript; Dr Jones conceptualized the study, drafted initial surveillance protocols, chaired the study expert panel, and substantially reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-2848

Accepted for publication Nov 4, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: At the time of publication, Dr Nissen was a full-time employee of GSK Vaccines; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The Australian Childhood Encephalitis study is funded by grants from the Australian Department of Health (Surveillance branch) and the National Health and Medical Research Council (NHMRC) of Australia Centre for Research Excellence in Critical Infections; both to Dr Jones and Dr Booy. Dr Britton is supported by an NHMRC postgraduate scholarship (1074547), the Royal Australasian College of Physicians (RACP) NHMRC Award for Excellence, and Norah Therese-Hayes/Sydney Medical School Dean's paediatric infectious diseases fellowship. Dr Elliott is supported by an NHMRC Practitioner Fellowship (1021480). Dr Dale is supported by an NHMRC Practitioner Fellowship (1059157). Dr Khandaker is supported by an NHMRC Health Early Career Fellowship (1054414).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2016;137;
DOI: 10.1542/peds.2015-2848 originally published online January 20, 2016;

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