Journal of Clinical Virology 173 (2024) 105664

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Full Length Article

Enterovirus and parechovirus meningoencephalitis in infants: A ten-year prospective observational study in a neonatal intensive care unit

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ARTICLE INFO

Keywords:
Neonatal encephalitis
Meningoencephalitis
Enterovirus
Parechovirus
Newborn
Brain mri
Neurodevelopment

ABSTRACT

Background: Non-polio enteroviruses (EV) and human parechoviruses (HPeV) are known etiological agents of meningoencephalitis in neonates. However, reports of neuroradiological findings and neurodevelopmental outcomes in this population are scarce.

Objectives: to describe clinical characteristics, neuroradiological findings and, in a subset of patients, neurodevelopmental outcomes in a cohort of infants with EV or HPeV meningoencephalitis within 60 days of life.

Study design: clinical/laboratory data, neuroradiological findings (cranial ultrasound, cUS, brain magnetic resonance imaging, MRI), and neurodevelopmental outcomes assessed by Ages and Stages Questionnaires – third edition were prospectively collected.

Results: overall, 32 infants with EV (21, 67.8 %) or HPeV (11, 28.2 %) meningoencephalitis were enrolled. Infants with HPeV (73 %: type 3 HPeV) presented more frequently with seizures (18.2 % *vs.* 0, p value=0.03), lymphopenia (1120 *vs.* 2170 cells/mm^3, $p = 0.02$), focal anomalies at electroencephalography (EEG) (63.6 *vs.* 23.8 %, $p = 0.03$), and pathological findings at MRI (72.7 % *vs.* 15.8 %, p value=0.004) compared to those affected by EV. cUS was not significantly altered in any of the enrolled infants. All infants with EV meningoencephalitis evaluated at 12–24 months and at 30–48 months were normal. Two out of the 7 infants with HPeV meningoencephalitis showed some concerns in gross motor (1/7, 14.3 %) or in problem solving (1/7, 14.3 %) function at 30–48 months of age.

Conclusions: In our cohort, neonates infected by HPeV had more severe clinical manifestations, more alterations at brain MRI, and some signs of long-term neurodevelopmental delay. Our data highlight the heterogeneity of manifestations in infants with EV or HPeV meningoencephalitis, and the need for long-term follow-up of those infected by HPeV in the neonatal period.

1. Background

Enteroviruses (EV) and human parechoviruses (HPeV) are ubiquitous, nonenveloped viruses with a single-stranded positive-sense RNA that belong to the picornaviridae family [1]. EV are classified into seven species infecting humans: three rhinovirus (RV) species (RV-A to RV-C) and four EV species (EV-A to EV-D). Besides Polioviruses, more than 110 serotypes have been typed, including coxsackieviruses (CVs) A and B and echoviruses (Es) [2]. Human parechoviruses (HPeVs) comprise up to 19 genotypes, with HPeV 1–3–6 being the most common [3]. In

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https://doi.org/10.1016/j.jcv.2024.105664
Received 3 October 2023; Received in revised form 29 February 2024;
Available online 5 March 2024

neonates and children below 5 years of age both EV and HPeV are a frequent cause of gastrointestinal, respiratory, or systemic infection [4,5], primarily during summer and fall in temperate areas, with a broad range of clinical severity [6,7]. EVs are isolated from cerebrospinal fluid (CSF) in up to 85–90 % of viral meningitis cases below 5 years of age [8,9], HPeVs being the second most common cause. In infants with EV or HPeV meningoencephalitis, cranial ultrasound (cUS) is mostly reported as normal or with rather unspecific abnormal findings [10]. Conversely, different patterns of brain involvement have been described using brain magnetic resonance imaging (MRI), such as widespread diffusion restriction in the white matter and the thalami [11] or punctate lesions in the periventricular white matter [10,12–14].

Neurodevelopmental outcomes after early life EV meningoencephalitis are not clearly defined [15,16]. The severity of neurodevelopmental impairment (NDI) after HPeV meningoencephalitis has been studied more frequently and seems affected by a great variability [17,18]. Nonetheless, two recent reports from the Netherlands [19] have shown good short-term outcomes after HPeV infection, especially applying the appropriate adjustments for confounding factors, but raised the concern for possible occurrence of gross motor function delay at longer term follow-up [20,21]. The correlation between MRI findings during or immediately after EV/HPeV meningoencephalitis in infants below 3 months of age and neurodevelopmental outcomes is largely unexplored.

2. Objectives

To describe clinical characteristics, neuroradiological findings and the neurodevelopmental outcomes in a cohort of infants with confirmed EV or HPeV meningoencephalitis occurred within 60 days of life.

3. Study design

3.1. Population and study procedures

This was a prospective, single-center observational cohort study enrolling infants aged 0–60 days admitted between 2009 and 2020 to the Neonatal Intensive Care Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, with a confirmed diagnosis of EV or HPeV meningoencephalitis. The study was conducted according to the guidelines of the Declaration of Helsinki of 1975, as revised in 2008, and was approved by the Institutional Review Board of the participating institution.

Infants were included if they had confirmed CSF positivity at molecular testing (see below) for EV or HPeV, with or without positivity for the same virus of other biological specimens. Exclusion criteria were the presence of congenital malformations, or a positive CSF culture for bacteria or fungi.

3.2. Case definitions

Viral meningoencephalitis [22–25] was diagnosed in the presence of 2 or more of the following symptoms: fever greater than or equal to 38 °C, mottled skin or prolonged refilling time (>3 s), abdominal distension, feeding intolerance, inappetence, diarrhea, bulging of anterior fontanel, irritability, crying exhaustion, significant alteration of muscular tone (hypotonia or hypertonia), lethargy, irritability, floppiness, or seizures, associated with a positive lumbar puncture for EV or HPeV in the absence of bacteria, fungi, and other viruses in the CSF itself. Pleocytosis of CSF was defined as $\geq$5 WBC/mm^3 [23].

3.3. Virological diagnostic tests

Until 2014, CSF samples were investigated for the presence of EV and HPeV RNA by means of RT-PCR (ELITechGroup, S.p.A, Turin, Italy for EV primers and Argene, Biomerieux-France for HPeV primers). Since 2015, CSF was analyzed using a multiplex real time-PCR (Fast Track Diagnostic FTD viral meningitis) assay. Starting from 2017, the FILMARRAY™ Meningitis/Encephalitis (ME) Panel was also introduced for the detection of nucleic acids from 14 bacteria, viruses and fungi. All enterovirus sequences were obtained using nested RT-PCR primers targeting a fragment of the VP1 gene (nt. 2602–2965) [26]. The molecular characterization of HPeV was performed by sequence analysis of the VP3/VP1 junction (nt. 2159–2458) specific for HPeVs [27]. Amplicons were purified using a NucleoSpin gel and PCR clean-up kit (Macherey-Nagel Gmbh & Co. KG, Duren, Germany) and were sequenced with a big-dye terminator cycle-sequencing kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA) in an ABI Prism 3130xl genetic analyzer (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

3.4. Cranial ultrasound (cUS) and brain magnetic resonance imaging (MRI)

Cranial ultrasound was performed by trained neonatologists according to local standard protocols. For brain MRI, each neonate was imaged on a 3T Achieva scanner (Philips Healthcare) using a 32-channel phased-array coil. We applied a scan-specific energy dose corresponding to 0.5 kJ/kg that varied according to the baby's weight [28]. The imaging protocol consisted of sequences performed for whole-brain evaluation: isotropic three-dimensional T1-weighted turbo spin-echo sequence (voxel size: 1 mm^3), axial and coronal T2-weighted turbo spin-echo sequence (repetition time/echo time: 5000/120 ms; slice thickness: 3 mm), axial diffusion weighted sequence. No contrast agent was used.

3.5. Electroencephalography (EEG)

A Micromed EEG device was used for neurophysiological brain monitoring at hospital admission, or at the onset of clinical symptoms in case of neonates already admitted to the ward [29]. To describe EEG patterns, a classification akin to the classification described by Murray et al. [30] was adopted.

3.6. Follow-up neurodevelopmental assessment

Ages and Stages Questionnaires – third edition (ASQ-3) were used to evaluate the acquisition of normal developmental milestones by enrolled infants [31]. For the present study, ASQ-3 were always completed by parents, either in front of the examining physician during follow-up visits, without any direct interaction with examining physician, or at home. ASQ-3 were administered at 12–24 months or 30–48 months of life.

3.7. Data collection and statistical analysis

Demographic and clinical data were retrieved from electronic medical records and collected in an electronic database. Statistically significant differences between infants with EV and HPeV infections were evaluated by means Mann-Whitney two-sided unpaired *U* test, for non-normally distributed linear variables (visually checked), or two-sided unpaired *t*-test for normally distributed linear variables. Binary or categorical variables were analyzed with Fisher's exact test. A probability value of $P < 0.05$ was considered as significant, without correction for multiple testing. Considered the similar baseline characteristics of neonates with EV and HPeV infection, cases were not matched for sex, gestational age, or age at infection. The correlation between brain MRI findings and nerudevelopment was assessed by logistic regression, with pathological MRI as the independent variable. Analysis and graphing was performed using Stata vers. 17.0 (StataCorp LLC). The present report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

4. Results

4.1. Clinical characteristics and laboratory parameters

Over the study period, 32 neonates with meningoencephalitis caused by EV or HPeV were enrolled. Among them, 21 (65.6 %) had a positive CSF RT-PCR for EV and 11 (34.4 %) for HPeV. Genotypes of EV and HPeV are reported in Fig. 1a-b. Seasonal distribution of cases was not significative for EVs, while HPeV infections were prevalent during summer and, with lower frequency, during the last 3 months of the year (Fig. 1c). Demographic and clinical characteristics of enrolled patients are shown in Table 1. None of the enrolled infants was born with a GA below 32 weeks. A significant proportion of parents reported respiratory symptoms in the days preceding the disease onset in their infant, while parental gastrointestinal symptoms were significantly more frequent in HPeV-infected neonates (36.4 % *vs.* 4.7 %, $p = 0.02$). Seizures were recorded in 18.2 % of infants with HPeV, but never in case of EV infection. Blood and CSF cell count and biochemical parameters were similar between the 2 groups, except for blood lymphocyte (significantly higher in infants with EV infection) and CSF pleocytosis, that was much more common in EV infection compared to HPeV (52.4 % *vs.* 18.2 %, $p = 0.06$). In total, 6 infants received empiric antiviral therapy (3 with EV and 3 with HPeV) with parenteral acyclovir, that was interrupted after molecular diagnosis on CSF, and no infant died.

4.2. Electroencephalography (EEG) and auditory brainstem responses (ABR)

EEG patterns at hospital admission were normal in 47.6 % of EV meningoencephalitis cases, mildly altered in 47.6 % and only in one case showed moderate alterations. No case of electrical seizures was recorded, but focal anomalies were recorded in 23.8 % of infants. Conversely, most neonates with HPeV infection presented focal anomalies in the frontal-temporal area (63.6 % overall, $p = 0.03$ *vs.* EV), and focal electrical seizures were recored in the 2 infants that were also presenting clinically detectable seizures (Table 2).

4.3. Brain imaging

All infants underwent cUS during hospitalization, but none showed specific abnormalities. Only 7 infants (5/21 infected by EV, 23.8 %, 2/11 infected by HPeV, 18.2 %) showed mild, bilateral, nonspecific periventricular hyperechogenicity (Table 2).

In 16/19 cases of EV meningoencephalitis MRI was normal, while 3 cases (15.8 %) showed single or few punctate lesions in the parietal periventricular white matter bilaterally, with a perivenular location and

Table 1
Baseline and clinical characteristics of infants with enterovirus (EV) or human parechovirus (HPeV) meningoencephalitis.

	EV	HPeV	*p value*
No. of neonates	21	11	
Male, n (%)	10 (47.6)	7 (63.6)	*0.39*
Gestational age, wks, median (range)	38 (32–40)	38 (36–40)	*0.91*
Gestational age <37 wks, n (%)	10 (47.6)	3 (27.3)	*0.45*
Birth weight, g, median (range)	3040 (880–3575)	3315 (2520–4170)	*0.09*
Days at symptoms onset, median (range)	8 (3–46)	10 (5–26)	*0.53*
Households with respiratory symptoms, n (%)	8 (38.1)	5 (45.5)	*0.68*
Households with gastrointestinal symptoms, n (%)	1 (4.7)	4 (36.4)	***0.02***
Fever >38°C, n (%)	16 (76.2)	11 (100)	*0.08*
Apnoea, n (%)	9 (42.9)	1 (9.1)	***0.05***
Dyspnea, n (%)	16 (76.2)	7 (63.6)	*0.45*
Mottled skin, n (%)	12 (57.1)	9 (81.8)	*0.16*
Delayed capillary refill time, n (%)	2 (9.5)	4 (36.4)	*0.06*
Hypotonia, n (%)	14 (66.7)	9 (81.8)	*0.36*
Drowsiness, n (%)	13 (61.9)	9 (81.8)	*0.25*
Feeding intolerance, n (%)	6 (28.6)	3 (27.3)	*0.94*
Vomiting, n (%)	3 (14.3)	0	*0.19*
Seizures, n (%)	0	2 (18.2)	***0.04***
CRP >1.5 mg/dL, n (%)	8 (38.1)	1 (9.1)	*0.08*
Neutrophils, cells/mm^3, median (range)	5325 (1440–10,600)	2910 (1570–8030)	*0.12*
Lymphocytes, cells/mm^3, median (range)	2170 (150–5620)	1120 (760–3570)	***0.02***
Platelets, cells/mm^3/1000, median (range)	297 (157–454)	216 (106–378)	*0.34*
Lactate, mmol/L, median (range)	2 (0.7–3.9)	2.3 (1.5–4.4)	*0.45*
Pleocytosis (>5 leukocytes/mL), n (%)	11 (52.4)	2 (18.2)	*0.06*
CSF leukocytes, cells/mm^3, mean (SD)	6 (0–1375)	2 (0–5)	*0.07*
CSF proteins, mg/mL, median (range)	72 (10–175)	55 (26–167)	*0.17*
CSF glucose, mg/dL, median (range)	49 (32–89)	56 (43–67)	*0.57*
Empiric antiviral therapy (acyclovir), n (%)	3 (14.3)	3 (27.3)	*0.37*

CSF: cerebrospinal fluid.

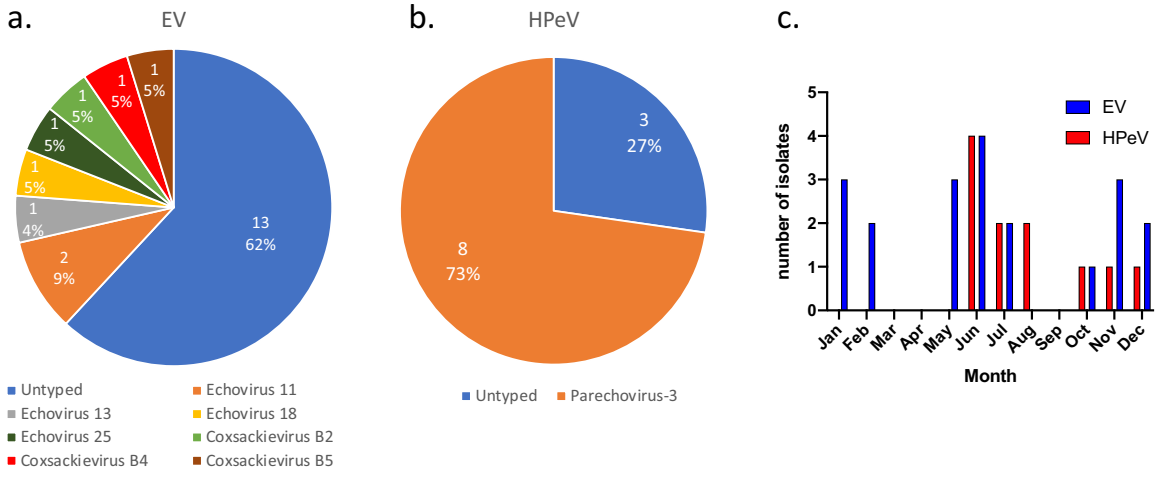

Fig. 1. a-b) Distribution of EV and HPeV genotypes of infected infants. c) seasonal distribution of EV and HPeV cases throughout the whole study period.

Table 2
Electroencephalography (EEG) data, brain imaging, and auditory brainstem responses (ABRs) in infants with enterovirus (EV) or human parechovirus (HPeV) meningoencephalitis.

	EV	HPeV	*p value*
EEG: background activity at onset	21	11	
0 (%)	10 (47.6)	3 (27.3)	*0.16*
1 (%)	10 (47.6)	5 (45.5)	
2 (%)	1 (4.8)	3 (27.3)	
3 (%)	0	0	
4 (%)	0	0	
EEG: focal anomalies at onset (%)	5/21 (23.8)	7/11 (63.6)	***0.03***
EEG: focal seizures at onset (%)	0	2/11 (18.2)	*0.16*
cUS performed (%)	21/21 (100)	11/11 (100)	
Abnormal findings **(%)**	0/21	0/11	*n.a.*
Brain MRI performed (%)	19/21 (90.5)	11/11 (100)	
Pathological findings **(%)**	3/19 (15.8)	8/11 (72.7)	***0.004***
- Single punctate T2 hypointense lesions (%)	2/19 (10.5)	2/11 (18.2)	*0.61*
- Multiple punctate T2 hypointense lesions (%)	1/19 (5.3)	6/11 (54.5)	***0.04***
- WM low signal on ADC sequences (%)	1/19 (5.3)	3/11 (27.3)	*0.12*
- Corpus callosum low diffusion coefficient (DWI,%)	0	2/11 (18.2)	*0.12*
ABRs performed (%)	10/21 (47.6)	5/11 (45.5)	*0.91*
Pathological findings	0	0	*n.a.*

cUS = cranial ultrasound; ADC = Apparent Diffusion Coefficient.

characterized by low signal on T2-weighted images (Fig. 2); in one of them (1/19, 5.3 %) the lesions also showed high signal on DWI and low apparent diffusion coefficient, suggestive for the sub-acute phase.

Among HPeV-infected infants, 8/11 (72.7 %) presented pathological findings at brain MRI (Fig. 3). In 6 out of the 8 cases multiple bilateral periventricular punctate WM lesions were observed: in 3 of them (2 HPeV type 3 and 1 HPeV untyped) the punctate lesions showed high signal on DWI and low apparent diffusion coefficient, and 2 out of the latter 3 cases also showed high signal of the corpus callosum on DWI. In the 2 remaining cases single punctate WM lesions were observed without signal changes on DWI.

4.4. Follow-up neurodevelopmental evaluation

Follow-up neurodevelopmental evaluation with ASQ-3 was obtained in 6/21 patients affected by EV, with 2 of them having repeated evaluations, and in 10/11 (91 %) of infants with HPeV meningoencephalitis. The remaining infants were lost to follow-up. Overall, 15 evaluations were performed at 12–24 months of age (median: 20 months), and 10 at 30–48 months of age (median: 36 months). All previously EV-infected infants performed normally at every domain of ASQ-3, including the 3 with pathological findings at MRI. Among infants with HPeV meningoencephalitis, all performed normally in all ASQ-3 domains at 12–24 months of age, but one (14.3 %) showed some concerns in gross motor functions and one (14.3 %) some concerns in problem solving at 30–48 months of age. The infant presenting concerns in problem solving had normal MRI findings during hospital admission, while the patient presenting gross motor function abnormalities had shown bilateral periventricular punctate lesions and restricted DWI at MRI examination 10 days after the onset of disease.

All other infants with MRI abnormal findings were normal at both neurodevelopmental evaluations. Logistic regression to evaluate the correlation between pathological brain MRI and adverse neurodevelopmental outcomes was not applicable to EV-infected infants (all with normal ASQ responses), and was not significant for HPeV-infected ones (odds ratio for adverse neurodevelopment in case of pathological brain MRI: 0.29, 95 % confidence intervals: 0.01 – 6.91, *p value*: 0.44).

5. Discussion

According to a recent report, EV and HPeV were detected in 14.1 % and 5.9 % of neonates and infants with fever without source, respectively [32]. Despite such a significant prevalence, neuroimaging presentation of these infections, neurodevelopmental outcomes, and the correlation between neuroimaging findings and outcomes in infants with EV or HPeV meningoencephalitis are largely unclear.

Here, we contribute to the field with a description of clinical findings, EEG patterns, neuroimaging, and neurodevelopmental evaluation of a cohort of 32 infants with EV or HPeV meningoencephalitis within the first 60 days of life.

The clinical presentation and laboratory values of our patients at hospital admission were mostly overlapping between infants infected by EV or HPeV, with some exceptions: neonates with EV presented more frequently with apnea and increased CSF white cells count, while in those with HPeV meningoencephalitis clinical seizures were much more common, albeit in the absence of significant CSF alterations. The CSF characteristics of our cohort are in line with those reported by de Ceano-Vivas et al. and de Jong et al. [16,33] and may guide clinicians in the

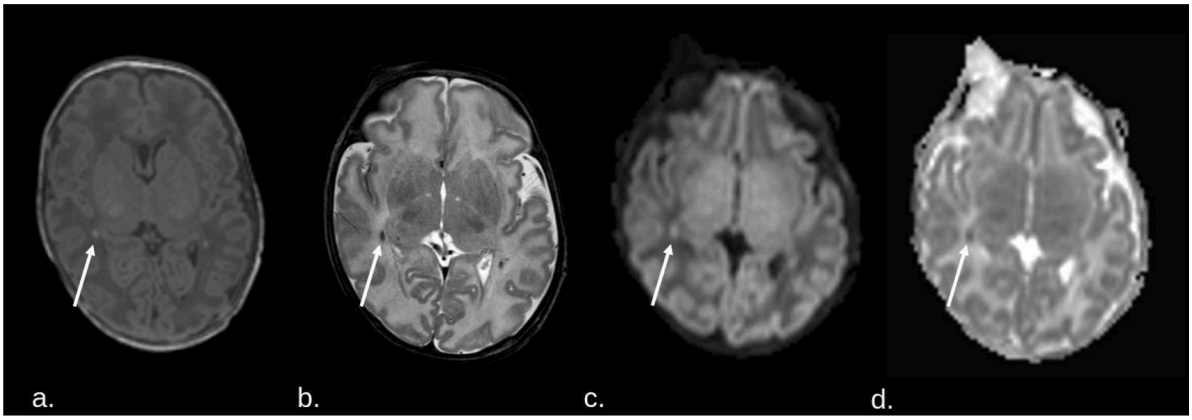

Fig. 2. Brain MRI imaging of a neonate with EV infection. Punctate periventricular white matter lesion (white arrow) with the following characteristic: a) hyperintensity in axial T1-weighted image b) hypointensity in T2-weighted image, c) high signal on DWI and d) low signal on ADC sequences. DWI: diffusion weighted imaging. ADC: apparent diffusion coefficient of water.

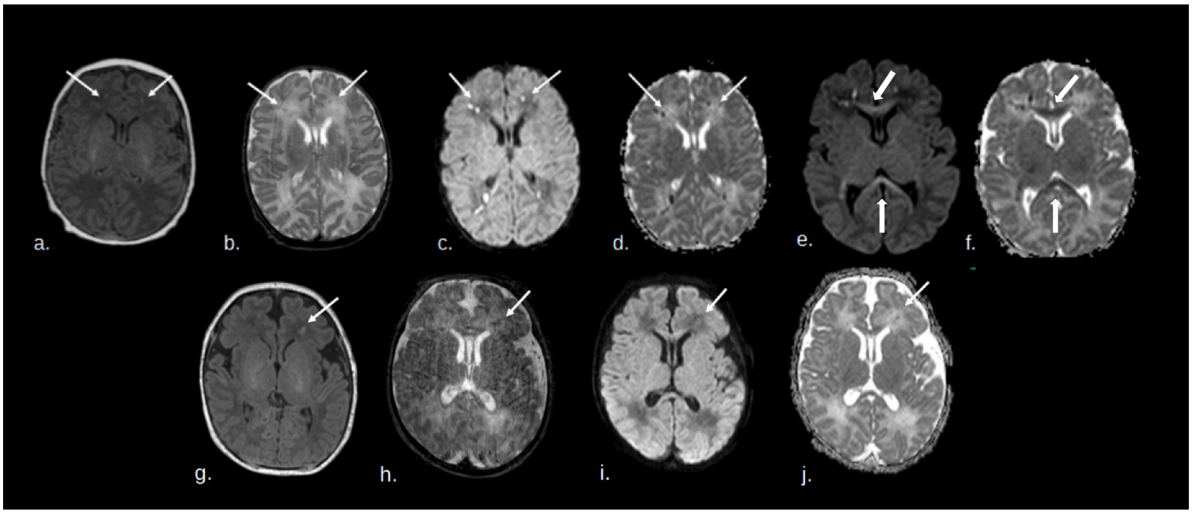

Fig. 3. Brain MRI imaging of 2 neonates with HPeV infection. a-f) Neonate with multiple bilateral punctate lesions in the periventricular white matter that appear a) hyperintense in axial T1-weighted image, b) hypointense in T2-weighted image, c) with high signal on DWI and d) with low signal on ADC sequences; in the same patient, corpus callosum lesions with e) high signal on DWI and f) low signal on ADC sequences coexisted. g-j) Neonate with isolated unilateral punctate lesion in the periventricular white matter that appear a) hyperintense in axial T1-weighted image, b) hypointense in T2-weighted image, c) with high signal on DWI and d) with low signal on ADC sequences. DWI: diffusion weighted imaging. ADC: apparent diffusion coefficient of water.

initial phase of diagnostic evaluation. The early discrimination between EV and HPeV infection might reveal important in the next future, if candidate therapeutic agents such as pleconaril will turn out to be clinically effective [34]. Interestingly, EEG patterns have not been described frequently in cases of neonatal EV or HPeV encephalitis. In our cohort, generalized slow background activity and focal anomalies were significantly more frequent in HPeV meningoencephalitis compared to EV-infected infants, and could be demonstrated in more than 50 % of patients. The EEG findings of our patients recall those typically described in cases of infant herpes simplex virus (HSV) encephalitis [35,36].

In our entire cohort of patients, cUS at disease onset revealed no pathological finding attributable to EV or HPeV infection, in line with most published literature [10,33,37]. The higher sensitivity of MRI allowed the identification of different types of CNS lesions in our patients. Punctate lesions, particularly within the frontal region WM or along the course of the deep medullary veins, have already been associated to both EV and HPeV encephalitis in infants, and might suggest viral neurotropism or, alternatively, vascular compromise (venous ischemia) [14]. Moreover, signal alterations at DWI are typical of acute inflammatory processes and have been previously reported in cases of EV and HPeV infection [13,14,38].

In a limited subset of our patients, we finally reported a neurodevelopmental evaluation acquired through the administration of ASQ-3, a tool with excellent sensitivity and specificity [39–41] for the identification of neurodevelopmental impairment (NDI) in pre-school aged infants and children [42]. Our results were reassuring for most screened patients, with 100 % of negative evaluations among infants infected by EV and the presence of some concerns for NDI in 2 infants affected by HPeV, one in the problem-solving domain at 18 months and one in gross motor function at 34 months of life. All the remaining evaluations were within the normal range, and logistic regression did not show any formal correlation between the results of brain imaging and the neurodevelopmental evaluation. Unfortunately, a significant proportion of enrolled infants was lost to follow-up for reasons beyond our control. Literature data regarding NDI after EV or HPeV meningoencephalitis during infancy are sparse, and frequently conflicting. For example, de Ceano-Vivas et al. recently reported the presence of some concern for NDI at the 18-month (median age) ASQ-3 in 48 % of patients previously experiencing EV CNS infection, compared to 20 % of those with HPeV, and the persistence of at least one altered domain 6–12 months later only in some infants with EV encephalitis [16]. Conversely, Silcock et al. recorded the presence of altered ASQ-3 results in more than 50 % of infants affected by HPeV encephalitis, with a partial improvement one year later [43]. This positive trend over time, however, has not been confirmed by van Hinsbergh et al., whose patients affected by HPeV encephalitis and tested through Bayley-3-NL and Movement Assessment Battery for Children version-2 (M-ABC-2-NL) presented worse gross motor function compared to EV-infected ones, with worse scores at 5 years than at 2 years from the infection [20]. Thus, the authors themselves underline the importance of long-term follow-up, at least until school age. We believe that our cohort was too small to draw definitive conclusion, but we agree with the need for longer term follow-up of these patients, which is currently ongoing. Interestingly, in our cohort pathological MRI findings during the 30 days after the onset of infection were not predictive of adverse outcomes at 2 or 3 years of age. With the important limitation of very small sample size, this is the first report associating MRI findings and neurodevelopmental outcomes after EV or HPeV meningoencephalitis in infants.

In summary, most infants in our cohort demonstrated favorable outcomes up to 4 years of life, including most of those presenting abnormalities at brain MRI examination. Larger, possibly multicenter studies with long-lasting and structured follow-up will support a rational prognostic evaluation and parental information regarding outcomes of EV and HPeV meningoencephalitis in infants.

Funding

This study received no specific funding.

CRediT authorship contribution statement

Carlo Pietrasanta: Writing – original draft, Investigation, Data curation, Conceptualization. **Andrea Ronchi:** Writing – review & editing, Investigation, Conceptualization. **Laura Bassi:** Writing – review & editing, Investigation, Data curation. **Agnese De Carli:** Writing – review & editing, Investigation, Data curation. **Luca Caschera:** Writing – review & editing, Investigation. **Francesco Maria Lo Russo:** Writing – review & editing, Investigation. **Beatrice Letizia Crippa:** Writing – review & editing, Investigation, Data curation. **Silvia Pisoni:** Writing – review & editing, Investigation. **Riccardo Crimi:** Writing – original draft, Investigation. **Giacomo Artieri:** Writing – review & editing,

Investigation. **Laura Pellegrinelli:** Writing – review & editing, Investigation. **Robertino Dilena:** Writing – review & editing, Investigation, Data curation. **Giorgio Conte:** Writing – review & editing, Investigation, Data curation. **Fabio Mosca:** Writing – review & editing, Resources, Conceptualization. **Monica Fumagalli:** Writing – review & editing, Investigation, Conceptualization. **Lorenza Pugni:** Writing – review & editing, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be available upon reasonable request to the corresponding author.

Acknowledgements

The Authors are grateful to ASGENAR (Associazione Genitori Neonati ad Alto Rischio ONLUS) for their precious support to the activity of the Infectious Disease research group of the Neonatal Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan.

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