

Enterovirus and parechovirus meningitis in infants younger than 90 days old in the United Kingdom and Republic of Ireland: a British Paediatric Surveillance Unit study

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Category: Original article

Keywords: Enterovirus, Parechovirus, Meningitis, Infants, Surveillance

Running title: Enterovirus and parechovirus meningitis

Abstract

Objectives

This study aimed to prospectively collect detailed clinical information for all enterovirus (EV) and human parechovirus (HPeV) meningitis cases in infants aged <90 days in the United Kingdom and Ireland.

Participants, design and setting:

Prospective, active national surveillance during July 2014/15 through the British Paediatric Surveillance Unit. Reporting paediatricians completed questionnaires requesting information on clinical presentation, investigations, management and outcomes at hospital discharge and after 12 months.

Main Outcome Measures:

To describe the clinical burden of EV and HPeV meningitis in infants aged <90 days.

Results

During the 13-month surveillance period, 703 cases (668 EV, 35 HPeV) were reported. The most common clinical presentations were fever (EV: 570/668 [85%]; HPeV: 28/35 [80%]), irritability (EV: 441/668 [66%]; HPeV: 23/35 [66%]) and reduced feeding (EV: 363/668 [54%]; HPeV 23/35 [66%]). Features of circulatory shock were present in 27% (182/668) of EV and 43% (15/35) of HPeV cases. Overall, 11% (76/668) of EV and 23% (8/35) of HPeV cases required intensive care support. Nearly all cases (678/703, 96%) were confirmed by cerebrospinal fluid (CSF) PCR, with 52% (309/600) having normal CSF white cell count for age. Two infants with EV meningitis died (2/668, 0.3%) and four survivors (4/666, 0.6%) had long-term complications at 12-months follow-up. Infants with HPeV meningitis survived without sequelae. 70% (189/270) had a formal hearing test, none had sensorineural hearing loss.

Conclusion

The incidence of laboratory-confirmed EV/HPeV meningitis in young infants is more than twice that for bacterial meningitis. Less than 1% will develop severe neurological complications or die of their infection. Further studies are required to formally assess long-term neurodevelopmental sequelae.

Introduction

Hospitalisation rates for childhood viral meningitis in England have increased year-on-year over the past decade, reaching 70 per 100 000 children in 2011, with the highest rates reported in infants younger than 90 days (1). This trend coincides with increasing routine use of molecular assays such as polymerase chain reaction (PCR) testing for viral infections in local hospital laboratories, which has led to a seven-fold increase in reports of laboratory-confirmed cases of viral meningo-encephalitis in the past decade (2). Enteroviruses (EV) accounted for half of nearly 10,000 reports and 92% of EV meningitis cases were reported in <3 month-olds (2). Human parechoviruses (HPeV) belong to the *Picornaviridae* family and can also cause viral meningo-encephalitis in infants, albeit less frequently than EV (3).

EV and HPeV usually cause mild, self-limiting respiratory and gastrointestinal infections in children. Occasionally, however, they may be responsible for more serious illness, including meningo-encephalitis, hepatitis, myocarditis or fulminant sepsis (4). Recent outbreaks associated with long-term neurological complications have been reported in Australia, northern Europe and USA (4–7). In neonates and young infants, viral meningitis can be difficult to diagnose and differentiate from more serious invasive bacterial infections because of their non-specific clinical presentation, especially in the early stages of illness (8,9), and lack of specific laboratory markers (10). Testing for EV/HPeV by clinicians and microbiologists across hospital laboratories is also variable because of differences in local protocols and limited understanding of clinical presentations, disease progression and outcomes. Additionally, there are no approved treatments for EV/HPeV infections and no investigational therapies undergoing clinical trials in Europe, in part due to lack of robust

data to support the need for effective therapeutics. The last UK publication on enterovirus epidemiology included retrospective data collected more than 20 years ago (11). We, therefore, undertook a prospective, population-based surveillance study to define the burden, clinical characteristics, investigations, management and outcomes of EV/HPeV meningitis in young infants across the UK and Republic of Ireland.

Methods

Surveillance

This study was conducted by Public Health England (PHE) and St. George's University of London through the British Paediatric Surveillance Unit (BPSU), a unique national clinical surveillance system set up to study rare diseases (12). The BPSU functions by sending paediatric consultants across the UK and Ireland a short electronic list of rare childhood conditions every month. All paediatricians are asked to respond and report whether they have seen a case (such as EV/HPeV meningitis) or confirm that they had no cases to report. Reporting is not compulsory but strongly encouraged, with regular reminders sent by the BPSU if no response is received. Following a positive report, the reporting paediatrician completes a detailed questionnaire on the case.

The study began on 01 July 2014 and continued for 13 months. A case was defined as a hospitalised infant aged <90 days at diagnosis with laboratory-confirmed EV/HPeV meningitis with clinical features of meningitis (fever $\geq 38^{\circ}\text{C}$, coma, seizures, neck stiffness, apnoea, bulging fontanelle, irritability, lethargy, poor feeding) and laboratory confirmation of EV/HPeV from any site (CSF, blood, stool, throat, peri-anal swab). The Second Generation Surveillance System (SGSS), a national electronic reporting system used by NHS laboratories

to notify clinically significant infections to Public Health England (PHE), was used as an alternative national data source for cases with EV/HPeV detected in the CSF in England, Wales and Northern Ireland. Additional cases identified through SGSS were followed-up in the same way as the BPSU-reported cases. Paediatricians who completed the clinical questionnaires were contacted after 12 months with a follow-up questionnaire on long-term outcomes.

Data analysis

Data were entered into Microsoft Access and analysed using STATA 14.0 (StataCorp, College Station, Texas). Table 1 outlines a full list of clinical definitions. Annual incidence was calculated using published live-births for each of the nations in 2014 after adjustment for the 13-month surveillance period. Data are mainly descriptive and summarised as medians with interquartile ranges or proportions, and compared using the Mann Whitney U test or the Chi squared or Fisher exact test, respectively. The binomial method was used to calculate the 95% confidence intervals (CI) for proportions.

Ethics Approval

The study has been approved by the London Queen Square research ethics committee (Ref: 14/LO/0229).

Results

During the 13-month surveillance period, 754 reports of EV/HPEV meningitis in infants aged <90 days were received and 703 (93%) fulfilled the case definition, including 668 (95%) with

EV meningitis and 35 (5%) with HPeV meningitis. The number of cases peaked in summer (**Fig 1**). The annual incidence of EV meningitis was 0.79 per 1,000 live-births and 0.04 per 1,000 live-births for HPeV meningitis. EV serotype information was available for 67% (448/668) of cases and included echovirus (54%, 242/448), coxsackie B5 (7%, 32/448), coxsackie B4 (6%, 28/448) and enterovirus 71 (4%, 17/448). None of the HPeV strains were typed.

The median age at diagnosis was 34 (IQR, 15 -53) days, and 58% (410/703 cases) were male. EV and HPeV cases were indistinguishable in terms of age distribution, clinical presentation and laboratory markers; none of the parameters were statistically significant (**Fig 2**). Among EV cases, fever ($\geq 38^{\circ}\text{C}$) was the commonest presentation (85%, 570/668), followed by irritability (66%, 441/668), reduced feeding (54%, 363/668) and lethargy (36%, 243/668). Fever was also the most common presentation in infants with HPeV meningitis (80%, 28/35) cases, followed by reduced feeding (71%, 25/35), irritability (66%, 23/35) and lethargy (51% 18/35) (**Fig 2**). On examination, the most common finding was circulatory shock in 27% (182/668) of EV and 43% (15/35) of HPeV cases, followed by respiratory distress (EV, 12% [79/668]; HPeV, 26% [9/35]) and rash (EV, 24% [163/668]; HPeV, 29% [10/35]). Of note, 17% (6/35) of infants with HPeV meningitis had abdominal distension and 11% (4/35) had a reduced Glasgow Coma Scale (<11/15) at presentation.

Intensive care admission

Most EV cases were admitted to the paediatric ward (78%, 522/668) or short-term assessment unit (9%, 59/668), while 11% required admission to a paediatric intensive care (PICU; 7%, 46/668) or high dependency unit (HDU; 4%, 30/668). Of the 35 HPeV cases, 23%

required PICU (17%, 6/35) or HDU (6%, 2/35) admission. Almost half the infants who presented in the first week of life (42%, 29/69) required PICU admission (**Table 2**). Half (50%, 23/46) the EV meningitis cases and all six HPeV cases in ICU required intubation and ventilation for a median of 5 and 4 days, respectively. A fifth (20%, 9/46) of EV meningitis cases and all HPeV cases required inotropic support. The most common EV serotypes responsible for PICU cases included echovirus 7 (n=4) and echovirus 9 (n=4), coxsackie B4 (n=3), echovirus 11 (n=3) and enterovirus 71 (n=1).

Diagnosis and investigation

Nearly all reported cases (96%, 678/703) were diagnosed through detection of virus in the CSF. The virus was also identified in the stool in 10% (69/703), blood in 5% (38/703) and throat swabs in 5% (34/703). Of those with reported CSF results, half the EV (51%, 304/600) and all HPeV (100%, 29/29) meningitis cases had less than 20 white cells per mm³ in the CSF. Most cases also had a normal peripheral blood white cell counts (6-15 x10⁹/L); EV: 85% (506/598) and HPeV: 56% (18/32). In addition, more than half the EV (56%, 360/643) and HPeV (67%, 22/33) cases had a CRP (C-reactive protein) level <10 mg/dL (**Fig 2**).

Six infants had coagulase-negative Staphylococci (CoNS) isolated from blood cultures (n=5) or CSF (n=1); all were considered to be contaminants and not treated with antibiotics.

In total, 8% (56/668) of EV and 29% (10/35) of HPeV meningitis cases had cranial ultrasound scans during admission. Relatively mild abnormalities were noted in five cases with EV meningitis (2 cases had resolving grade 1 IVH and 3 cases small choroid plexus bleeds with normal parenchyma). Overall, 3% (17/668) of EV meningitis cases had an MRI head scan

during admission and eight were abnormal (white matter changes [n=3], and one case each of subdural haemorrhage, posterior fossa blood collection, acute infarct in the right corona, severe cystic encephalomalacia and mild ventricular dilatation).

Treatment and outcomes at hospital discharge

A significant proportion of cases were treated with acyclovir in addition to empiric intravenous antibiotics (EV meningitis 27% 183/668; HPeV meningitis 46%, 16/35). The median duration of acyclovir treatment was 3.1. days. Three EV and one HPeV cases were also treated with intravenous immunoglobulin; the indication for administering immunoglobulin was not stated. Two infants with EV meningitis died (2/668; case fatality rate, 0.3%; 95% CI, 0.04-1.1%). Of the survivors, two had significant neurological sequelae at hospital discharge, which were still present at 12 months follow-up (Table 2). None of the infants with HPeV meningitis died and one had transaminitis at hospital discharge, which resolved spontaneously. Prematurity status, age at diagnosis and EV serotype were not associated with more severe clinical presentation or poor outcome at discharge.

Follow-up at 12 months

Follow-up questionnaires were sent to all paediatricians who had reported a case. In total, 38% (254/668) of EV and 46% (16/35) HPeV infants were reviewed by the clinical team on at least one occasion during 12 months after hospital discharge. Of these, 70% (189/270) had a formal hearing test after discharge from hospital and none of those tested had sensorineural hearing loss. At follow-up, two additional infants with EV meningitis, who were well at discharge, were identified with neurological complications by 12 months. The

risk of long-term sequelae among infants with EV meningitis who were followed up was 0.6% (4/666; 95% CI, 0.2-1.5%) (Table 3).

Discussion

We have reported the largest prospective national study to evaluate the burden, clinical characteristics and outcomes of EV/HPeV meningitis in young infants during a period devoid of local or national outbreaks. We found some evidence of more severe disease in infants with HPeV compared to EV meningitis, with higher rates of circulatory failure, PICU admission and requirement for multi-organ support. Two of the 668 infants with EV meningitis died and four others had long-term neurodevelopmental complications at 12 months follow-up, while the small number of infants with HPeV meningitis recovered without complications

The incidence of laboratory-confirmed EV/HPeV meningitis is >2-fold higher than recent estimates for bacterial meningitis in the same age-group (0.38/1000 live births) using the same surveillance methodology (13). This incidence is also >5 times higher than group B streptococcal meningitis, currently the single most important cause of bacterial meningitis in young infants (13). Our estimates are, however, likely to be significantly under-estimated for several reasons. Infants with EV/HPeV meningitis often have normal peripheral white cell counts and CRP levels, which can reassure clinicians against further investigations. Even when lumbar puncture is performed, more than half do not exhibit CSF pleocytosis, and, therefore, may not undergo further testing for viruses (8). Many hospital laboratories only test CSF samples for viruses in the presence of CSF pleocytosis and negative bacterial

cultures. As multiplex PCR-testing becomes more established, however, laboratories are increasingly testing all CSF samples routinely for viruses, especially in infants. This in part explains the rapidly increasing reports of EV/HPeV infections in England in recent years (2).

Another major consideration is that 96% of cases were diagnosed through virus detection in the CSF. Paediatricians need to be aware that some of these viruses may only be detected at a peripheral site, such as the upper respiratory tract, blood or stools; specimens from these sites should, therefore, also be routinely tested in infants with suspected meningitis (14). Rapid diagnosis will help rationalise antimicrobial use, guide additional investigations, support early hospital discharge and reassure parents about long-term outcomes (15,16).

The finding that nearly 10% of cases were diagnosed within the first week of life, without any particular association with EV/HPeV type, suggests transplacental transmission in this cohort because of the relatively short interval between birth and illness; transplacental transmission has been demonstrated in a previous prospective cohort study which identified echovirus 11 from the respiratory or gastrointestinal tract of 4 out of 7 infected neonates by three days of age and also in their mothers at term (17). The lack of CSF pleocytosis in half the cases has been reported in the literature but is not widely known among clinicians and microbiologists. In a recent, retrospective South Korean study involving 390 children with EV meningitis, 16-18% did not have CSF pleocytosis, but this proportion increased to 68-77% in neonates; young age, lower peripheral WBC count and shorter interval between illness onset and lumbar puncture were associated with the absence of CSF pleocytosis (18). Our study highlights the importance of performing lumbar

punctures in unwell young infants with non-specific presentations and routinely testing for EV/HPeV in the CSF and other sites.

Viral meningitis is generally associated with good outcomes but there is a paucity of robust follow-up data for infants. We, for the first time, are able to reliably estimate the low but significant risk of serious outcomes in young infants with EV/HPeV meningitis, supporting some of the previous studies (19) (20), although others have reported no (21–23) or only mild (24) complications at follow-up. Most of these studies were conducted >20 years ago, used crude developmental assessment tools at inconsistent times after the acute illness and evaluated small numbers of infants. Notably, in our cohort, although only 38% of infants underwent audiological testing after hospital discharge, none had hearing loss, which is in keeping with another recent UK national surveillance of 106 infants with HPeV and supports current consensus that audiological follow up after hospital discharge in infants with EV and HPeV meningitis is not routinely required in infants who are otherwise well at hospital discharge (25).

HPeV represented a small proportion of our cases, partly because HPeV infections peak every two years and this study was conducted in a year of low HPeV activity (4,26,27). Additionally, many hospital laboratories still do not routinely test for HPeV, even those that routinely test for EV, although an increasing number of hospital laboratories have been adding HPeV testing to their existing multiplex PCR assays recently (28).

Several studies have reported significant long-term neurodevelopmental sequelae in infants with HPeV meningitis, especially associated with HPeV type 3 (29) (30). These studies,

however, often reported a small and highly selective group of infants with very severe clinical presentations, but they do highlight the potential for this virus to cause permanent irreversible neurological damage. These results also question whether those with less severe clinical presentations might go on to develop subtle long-term complications that remain undetected.

Additional robust long-term neurodevelopmental studies with larger numbers of cases are required to provide an evidence base for management of infants with viral meningitis beyond hospital discharge.

The strength of this study lies in the prospective national surveillance that captured all cases across the UK and Ireland over a relative short time period. A limitation of our study is the low proportion of EV/HPeV strains submitted for typing to the PHE reference laboratory (31); we were, therefore, unable to assess correlations between serotype and poor outcomes, which were rare. Additionally, as there are currently no evidence-based guidelines, clinical investigations and management as well as outpatient follow-up of infants was haphazard, with only 30% of infants reviewed after hospital discharge. It is, therefore, possible that our estimate of long-term complications may be underestimated

In conclusion, the incidence of laboratory-confirmed EV/HPeV meningitis in young infants is more than twice that for bacterial meningitis in the UK and Ireland. Around 1% of infants will develop significant complications or die of their infection. Further studies are required to determine long-term neurodevelopmental sequelae in infants who are well at hospital discharge. Clinicians should consider formal neurodevelopmental assessment in infants with

persistent symptoms, and those with severe neurological presentations and/or abnormal neuroimaging findings during the acute illness.

What's known on this subject:

- Enterovirus and human parechovirus are common causes of infant meningitis.
- The clinical burden of disease is unknown due to a lack of robust epidemiological data.
- No antiviral or vaccines are licenced in Europe or the USA to treat or prevent disease.

What this study adds:

- In UK infants, the combined incidence of EV (0.79/1,000 live-births) and HPeV (0.04/1,000 live-births) meningitis is more than double that for bacterial meningitis
- More than half the infants had absent CSF pleocytosis and low inflammatory markers.
- Less than 1% of infants developed significant complications or died of their infection.

Funding: none declared.

Contributors S.K and S.L conceptualised and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. S.B and S.R designed the data collection instruments, collected data and reviewed and revised the manuscript.

D.J.A, R.C, R.P, D.B and M.S conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

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Parameter	Definition
Early-onset	0-6 days
Late-onset	7-89 days
Preterm	<37 weeks gestation
Term	≥37 weeks
CSF pleocytosis	>20 white cells per mm ³ (32)
Features of circulatory shock included any combination of hypotension, mottled skin, capillary refill time >2 seconds, tachycardia >160 beats/min and/or reduced urinary output <2mls/kg/hr.	

Table 1: Definitions of demographic and clinical parameters

	Age at diagnosis			
	0-6 days	7 – 28 days	29 – 89 days	All cases
Virus:				
EV	64 (91)	207 (94)	372 (96)	643 (95)
HPeV	6 (9)	13 (6)	15 (4)	34 (5)
Site of admission:				
PICU	29 (42)	16 (7)	7 (2)	52 (8)
HDU	5 (7)	15 (7)	12 (3)	32 (4)
Ward	35 (51)	169 (74)	335 (86)	539 (79)
PAU	0	29 (13)	34 (9)	63 (9)
Clinical presentation:				
Fever	49 (68)	186 (83)	342 (90)	577 (34)
Irritability	26 (36)	146 (65)	277 (73)	449 (26)
Lethargy	33 (45)	88 (39)	130 (34)	251 (15)
Reduced feeding	35 (49)	121 (54)	211 (55)	367 (21)
Respiratory distress	19 (26)	32 (14)	23 (6)	74 (4)
Laboratory findings:				
WCC	10.3 (8.0 – 14.7)	9.8 (3.9 – 20.8)	9.3 (7.2 – 12)	9.8
Neutrophil	6.8 (4 – 10.7)	4.6 (3.5 – 6.8)	4.1 (2.9 – 6)	5.1
CRP	14 (5 – 25)	11 (4 – 22)	8 (3.9 – 16.8)	11
CSF WCC	14 (5 – 25)	8 (2 – 102)	26 (2 – 122)	9
6 (2 – 32)				
Outcome at discharge:				
Recovered	65 (97)	202 (98)	340 (98)	607 (98)
Sequale	2 (3)	3 (1)	8 (2)	13 (2)
Died	0	2 (1)	0	2 (0)
Serotype				
Coxsackie B4	4 (10)	8 (6)	16 (6)	28 (7)
Coxsackie B5	1 (2)	11 (8)	20 (7)	32 (8)
Echovirus 7	3 (7)	12 (9)	24 (9)	39 (10)
Echovirus 9	9 (22)	18 (13)	48 (18)	75 (20)
Echovirus 11	4 (10)	3 (2)	12 (4)	19 (5)
Echovirus 18	4 (10)	13 (9)	26 (10)	43 (12)
Echovirus 25	3 (7)	4 (3)	18 (7)	25 (6)
Echovirus 30	1 (2)	7 (5)	9 (3)	17 (4)
Enterovirus 71	1 (2)	10 (7)	6 (2)	17 (4)
Untyped	5 (12)	33 (24)	55 (21)	93 (24)

Data are presented as numbers of cases (%)

Table 2: Characteristics of infants aged <90 day with EV and HPeV meningitis in the United Kingdom and Ireland during July 2014 to July 2015 inclusive

EV= enterovirus; HPeV = Human parechovirus; PICU = Paediatric intensive Care Unit; HDU = High Dependency unit; PAU=Paediatric Assessment Unit; CSF = Cerebrospinal fluid; WCC = white cell count; CRP = C reactive protein

	Presenting features	Admission to Intensive Care	Neuroimaging findings	Outcome at hospital discharge	Outcome at 12 months
EV deaths					
Born at term <1 week old EV11 infection	Afebrile, lethargic, reduced feeding; developed multi-organ failure and shock. CRP 6, CSF WCC clotted	Intubated & ventilated (13 d), inotropes (12 d); IV corticosteroids + IVIG	Cranial ultrasound scan normal; echocardiogram – mitral valve regurgitation and valvulitis	Died after 2 weeks of massive pulmonary haemorrhage	
Born at term 1 month EV (not typed)	Reduced feeding; circulatory collapse; rapid deterioration CRP 52; CSF WCC 0	Intubated & ventilated (1 d), inotropes (1 d)	Not performed	Died within 48 hours; EV isolated from heart and brain tissue at post mortem	
EV sequelae					
Premature (33-36 wks) 1 month old EV11 infection	Respiratory distress, apnoea CRP 4.6, CSF WCC 0	Intubated & ventilated (1 d), inotropes (2 d), haemofiltration (1d)	MRI: diffuse encephalitis and microcephaly.	Reduced tone trunk, increased tone in the limbs	Reduced vision, reduced truncal tone, increased tone in the limbs; seizures
Born at term <1 week old Coxsackie B4 infection	Fever, irritability, respiratory distress, bulging fontanelle, cardiovascular shock CRP 45, CSF WCC 20	Intubated & ventilated (35 d) ionotropic support; 1 dose IVIG	MRI: acute infarction, right anterior corona	Poor ventricular function requiring medical treatment	Poor ventricular function, on captopril
HPeV sequelae					
Born at term 1 week old HPeV (not typed)	Irritability poor feeding, respiratory distress, signs of shock CRP 8, CSF WCC 2	Not admitted	Not performed	Transaminitis (normal abdominal ultrasound) at discharge	Well
12 month follow-up					
Premature (28-32 wks) 1 month old EV (not typed)	Lethargy, reduced feeding, apnoea CRP 5, CSF WCC 13	Intubated & ventilated (5 d),	MRI: severe cystic encephalomalacia, multiple fluid filled cysts in frontal, parietal & temporal lobes	No clinical symptoms or signs	Seizures controlled on anti-epileptics
Born at term 1 week old EV (not typed)	Fever, irritability, rash, seizure; CRP 99; CSF WCC 90	Not admitted	Cranial ultrasound normal	Well at discharge	Tonic clonic seizures; not on regular anticonvulsants

Table 3. Death and Sequelae among infants aged <90 days with enterovirus (EV) and human parechovirus (HPeV) meningitis in the United Kingdom and Ireland during July 2014 to July 2015 inclusive. IVIG, intravenous immunoglobulin; CRP, c-reactive protein.mg/dl; CSF WCC, cerebrospinal fluid white cell count/per mm³;