Cytowanie: Śladowska J, Piwowarczyk A, Kuchar E: Zapalenie mózgu wywołane przez parechowirusa o przebiegu zbliżonym do sepsy u niemowląt – seria przypadków. Pediatr Med Rodz 2023; 19 (4): 437–441. DOI: 10.15557/PiMR.2023.0067.

Julia Śladowska[1], Anna Piwowarczyk[2], Ernest Kuchar[2]

Otrzymano: 27.07.2023
Zaakceptowano: 06.12.2023
Opublikowano: 29.12.2023

Zapalenie mózgu wywołane przez parechowirusa o przebiegu zbliżonym do sepsy u niemowląt – seria przypadków

Sepsis-like HPeV encephalitis in young infants – case series

[1] Wydział Lekarski, Warszawski Uniwersytet Medyczny, Warszawa, Polska
[2] Klinika Pediatrii z Oddziałem Obserwacyjnym, Warszawski Uniwersytet Medyczny, Warszawa, Polska
Adres do korespondencji: Julia Śladowska, Wydział Lekarski, Warszawski Uniwersytet Medyczny, Żwirki i Wigury 61, 02-091 Warszawa, Polska, e-mail: j.sladowska1@gmail.com

https://doi.org/10.15557/PiMR.2023.0067

ORCID iDs
1. Julia Śladowska https://orcid.org/0000-0003-3560-3867
2. Anna Piwowarczyk https://orcid.org/0000-0002-8764-7442
3. Ernest Kuchar https://orcid.org/0000-0002-7883-2427

Streszczenie

Ludzki parechowirus jest częstym czynnikiem etiologicznym zapalenia mózgu u niemowląt do 3. miesiąca życia, jednak jego rozpoznanie jest niedoszacowane. Na podstawie retrospektywnej analizy dokumentacji medycznej 5 niemowląt w pracy scharakteryzowano objawy, wyniki badań laboratoryjnych oraz potencjalne czynniki ryzyka parechowirusowego zapalenia mózgu o przebiegu zbliżonym do sepsy. Definicja przypadku została oparta na objawach neurologicznych, dodatnim wyniku badania PCR (*polymerase chain reaction* – łańcuchowa reakcja polimerazy) płynu mózgowo-rdzeniowego w kierunku parechowirusa oraz kryteriach klinicznych rozpoznania sepsy zaproponowanych przez National Institute for Health and Care Excellence (NICE). Najczęstszymi objawami były: drażliwość, gorączka, nieprawidłowe napięcie mięśniowe, marmurkowanie skóry, zmniejszona aktywność, tachykardia, wzdęcie/tkliwość w obrębie jamy brzusznej oraz brak odruchów noworodkowych. W badaniach płynu mózgowo-rdzeniowego nie stwierdzono odchyleń od wartości referencyjnych. Badania laboratoryjne krwi wykazały limfopenię, leukopenię i niedokrwistość. Uzyskane wyniki wskazują na konieczność wykonywania badania PCR w kierunku parechowirusa u niemowląt z klinicznymi cechami sepsy i objawami neurologicznymi, mimo braku zmian zapalnych w płynie mózgowo-rdzeniowym.

Słowa kluczowe: neuroinfekcja, odporność noworodkowa, objawy neurologiczne, objawy ogniskowe

Abstract

Human parechovirus is the most common underrecognised aetiological agent of encephalitis in children younger than 90 days. The aim of this study is to describe the clinical manifestation, laboratory features, and potential risk factors for severe parechovirus-related sepsis-like encephalitis. The case series included five infants aged below three months diagnosed with sepsis-like parechovirus encephalitis. The diagnosis was based on the patients' neurological symptoms, the criteria of sepsis defined by the National Institute for Health and Care Excellence, and parechovirus-positive cerebrospinal fluid polymerase chain reaction (PCR). The majority of patients presented with irritability, fever, abnormal muscle tone, mottling, decreased activity, tachycardia, abdominal distension, and absence of neonatal developmental reflexes. No abnormalities in the cerebrospinal fluid were identified. Abnormal blood laboratory measurements included lymphopaenia, leukopaenia, and anaemia. The case series highlights the necessity to perform cerebrospinal fluid PCR for parechovirus in infants with sepsis-like illness and neurological signs but without cerebrospinal fluid signs of inflammation.

Keywords: neuroinfection, neonatal immunity, neurologic signs, focal signs

INTRODUCTION

Human parechoviruses (HPeVs) are non-enveloped, single-stranded RNA viruses classified in the genus *Parechovirus* of the family *Picornaviridae*[1]. Nowadays, there are 19 identified types of HPeV. They cause a spectrum of diseases ranging from self-limiting febrile illness and respiratory symptoms to sepsis-like illness, myocarditis, encephalitis, and sometimes, death[1]. A severe course of HPeV infection is mostly seen in newborns and young infants; nevertheless, neither of the perinatal factors was found to be associated with the risk of HPeV infection[2]. Although HPeV statistics have not yet been officially published, clinicians and public health departments have been observing a growing prevalence of this infection. The case series presented below aims to characterise the epidemiology, clinical features, and potential risk factors of sepsis-like HPeV encephalitis.

METHODS

The medical records of infants younger than three months, diagnosed with sepsis-like HPeV encephalitis at three hospitals in Warsaw, Poland, between May 2022 and August 2022, were retrospectively reviewed.

The initial diagnosis of encephalitis was based on the definitions used in the UK-ChiMES (Childhood Meningitis and Encephalitis) and ENCEPH-UK studies[3]. Inflammation of the central nervous system (CNS) was confirmed by the positive result of rapid multiplex polymerase chain reaction (PCR) from cerebrospinal fluid (CSF) for common viral, bacterial, and yeast pathogens (FilmArray Meningitis/Encephalitis Panel, BioFire Diagnostics, USA) and, additionally, abnormalities visible on magnetic resonance imaging (MRI). Positive HPeV PCR results were not sequenced for genotyping of the viral agents.

Patients with encephalitis who met at least two high-risk criteria for sepsis defined by the National Institute for Health and Care Excellence (NICE) (Tab. 1) were recognised as having a sepsis-like course of encephalitis[4].

Patients with uncertain aetiology of sepsis due to bacterial or viral coinfection were excluded from the study.

The medical records of the infants were analysed primarily for perinatal data, family history, clinical examination, results of laboratory tests, and medications.

The calculations shown below were performed using Microsoft Excel 2019.

RESULTS

In Warsaw, between May and August 2022, a total of five patients with a sepsis-like course of HPeV encephalitis were identified in the group of 16 patients diagnosed with HPeV encephalitis. The clinical and laboratory data of individual patients are summarised in Tab. 2.

The median age of the patients was 27 days (range: 8–58 days). There was a great disproportion between boys and girls (male: 5, female: 0). All the infants were delivered at term, primarily (n = 4) by the vaginal route, and all were breastfed since birth. The infants were born to mothers aged from 21 to 38 years old (median: 35 years old). All the patients were second-borns, and the median age gap to the sibling was 2.5 years (range: 2–3.5 years). Ill household contact was reported in three cases; nevertheless, we did not test symptomatic family members for

Category	High risk criteria	Moderate to high risk	Low risk criteria
Behaviour	• No response to social cues • Appears ill to a healthcare professional • Does not wake, or if roused does not stay awake • Weak high-pitched or continuous cry	• Not responding normally to social cues • Wakes only with prolonged stimulation • Decreased activity • Parent or carer concern that child is behaving differently from usual	• Responds normally to social cues • Content or smiles • Stays awake or awakens quickly • Strong normal cry or not crying
Cardiovascular system	• Heart rate 160 beats per minute or more • Heart rate less than 60 beats per minute	• Heart rate 150–159 beats per minute • Capillary refill time of 3 seconds or more • Reduced urine output, or for catheterised patients passed less than 1 mL/kg of urine per hour	• No high risk or moderate to high risk criteria met
Respiratory system	• 60 breaths per minute or more • Grunting • Apnoea • Oxygen saturation of less than 90% in air or increased oxygen requirement over baseline	• 50–59 breaths per minute • Oxygen saturation less than 92% in air or increased oxygen requirement over baseline • Nasal flaring	• No high risk or moderate to high risk criteria met
Integumentary system	• Mottled or ashen appearance • Cyanosis of skin, lips or tongue • Non-blanching rash of skin	• Pallor of skin, lips or tongue	• Normal colour
Temperature	• Aged under 3 months: 38°C or more • Any age: less than 36°C	• Aged 3–6 moths: 39°C or more	
Other (regardless of age)		• Leg pain • Cold hands and feet	

Tab. 1. Sepsis risk stratification tool: children aged under one year in or out of hospital based on the National Institute for Health and Care Excellence (NICE) guidelines[4]

DOI: 10.15557/PiMR.2023.0067

Variable		Infant 1	Infant 2	Infant 3	Infant 4	Infant 5
Age at onset (days)		8	27	8	58	27
Ill household contact aged <3 years		No	No	No	No	Brother with upper respiratory tract infection
Ill household contact aged >3 years		Father with herpes labialis	No	Father with upper respiratory tract infection	No	Mother with fever, abdominal distension, and weakness in legs
Fever >38°C		Yes	Yes	Yes	No	Yes
Cardiovascular system		Tachycardia	Tachycardia, oedema, cyanosis, mottled skin, CRT >2 s	Tachycardia	Tachycardia, mottled skin	Tachycardia, mottled skin
Respiratory system		Tachypnoea, grunting, apnoea	Grunting	Tachypnoea	No	No
Nervous system		Decreased activity, irritability, poor neonatal developmental reflexes	Decreased activity, irritability, hypotonia, meningeal signs, poor neonatal developmental reflexes	Decreased activity, irritability, hypotonia, poor neonatal developmental reflexes	Irritability, hypertonia	Irritability, hypertonia
Integumentary system		Erythema on the neck	Maculopapular rash	No	Café au lait spot	No
Gastrointestinal system		Abdominal distension, jaundice	Abdominal distension	Abdominal distension, jaundice	Abdominal distension	Abdominal distension, vomiting
CSF results	Cytosis [cells/μL]	-*	6	-*	10	2
	Glucose [mg/dL]	-*	43	50	47	52
	Protein [mg/dL]	-*	42.7	109.5	33	44.2
CBC results	WBC [10^3/μL]	6.64	4.03	5.55	11.3	4.88
	LYM [10^3/μL]	0.86	1.58	1.1	8.65	1.22
	RBC [10^6/μL]	4.15	3.74	4.25	3.92	3.24
	HGB [g/dL]	14.4	12.1	15.2	12.1	11.2
	HCT [%]	40.6	33.9	45.4	33.8	30.9
	MCV [fl]	97.8	90.6	98.1	86.2	95.4
	INR	1.42	1.14	0.84	1.25	-*
	APTT [sec]	49.54	46.28	53.04	51.84	49.62
	AST [U/L]	48	164	29	444	52
	ALT [U/L]	22	133	15	151	14

* Test was not performed.
ALT – alanine aminotransferase; **APTT** – activated partial thromboplastin time; **AST** – aspartate aminotransferase; **CBC** – complete blood count; **CRT** – capillary refill time; **CSF** – cerebrospinal fluid; **HCT** – haematocrit; **HGB** – haemoglobin; **INR** – international normalised ratio; **LYM** – lymphocytes; **MCV** – mean corpuscular volume; **RBC** – red blood count; **WBC** – white blood count.

Tab. 1. Description of HPeV-positive infants suspected of sepsis

HPeV. The median length of stay was six days (range: 6–8 days).

All the patients presented with tachycardia, defined as heart rate ≥160 beats/minute[4], irritability, and abdominal distension. Four presented with acute onset of fever >38°C persisting between three to four days, and one remained subfebrile. Among the patients with cardiovascular symptoms, two presented only with mottling of the extremities and Infant 2 developed >2 signs of circulatory failure. Respiratory symptoms suggestive of sepsis included grunting (n = 2), respiratory rate ≥60 breaths/minute (n = 2)[4], and apnoea (n = 1). All the infants included in the study were irritable, but decreased activity (difficulties in awakening for feeding), poor neonatal developmental reflexes, and the presence of meningeal signs were observed in three cases. Other neurological abnormalities included hypotonia (n = 2) and hypertonia (n = 2). Additional clinical manifestations of HPeV infection observed in the patients included skin symptoms (n = 3), jaundice (n = 2), and vomiting (n = 1).

CSF specimens were all positive only for HPeV. CSF analysis was not performed in Infant 1 due to a laboratory mistake. One specimen (from Infant 2) was not analysed for CSF leukocytes. CSF pleocytosis, defined as CSF leukocytes >20 cells/μL (following the standards of the hospital laboratory) was not found in any patient. CSF glucose (N: >20 mg/dL) and CSF protein (N: <150 mg/dL and <58 mg/dL in infants younger and older than 10 days, respectively)[5] were within the reference ranges in all the patients.

Abnormal laboratory measurements in the neonates (Infants 1, 2, 3, 5) included white blood cell count <6 × 10^3/μL (n = 3), lymphocytes <2.8 × 10^3/μL (n = 4), red blood cell count <3.9 × 10^6/μL (n = 2), haemoglobin <13.4 g/dL (n = 2), haematocrit <41% (n = 3), activated partial thromboplastin time (APTT) >50 seconds (n = 1), and both aminotransferases (aspartate and alanine aminotransferases) >100 U/L (n = 1)[6].

 DOI: 10.15557/PiMR.2023.0067

Laboratory measurements in the two-month-old patient (Infant 4) were assessed according to the age-appropriate standards. The deviations found in the infant included elevated levels of APTT and both aminotransferases[6].

MRI was performed in all the infants, cranial ultrasound in Infants 1, 3, and 5, and electroencephalography (EEG) in Infant 1 only. MRI revealed small white matter lesions in two patients (Infants 1 and 4). Cranial ultrasound and EEG showed no abnormalities in any infants subjected to examination.

Based on the clinical presentation mimicking sepsis, the infants received intravenous fluids (n = 5), ampicillin and gentamicin (n = 4), and acyclovir (n = 2) at admission. Among the patients treated with antibiotics, Infants 1, 2, and 3 discontinued treatment on the second day of hospitalisation, and Infant 5 discontinued gentamicin on the third and ampicillin on the fourth day after obtaining negative urine culture. Acyclovir was administered due to a severe course of the disease (Infant 2) or the risk of herpes simplex virus transmission from the symptomatic parent (Infant 1). Additionally, Infant 2 received a human albumin solution for circulatory decompensation. No corticosteroids or other immunosuppressants were used.

All the patients were discharged without neurological sequelae.

DISCUSSION

In accordance with prior investigations, the above data are consistent with the common signs of HPeV neuroinfection, including tachycardia, abdominal distension, irritability, fever and abnormal muscle tone[1,7]. In all febrile patients, defervescence was associated with an improvement in the general condition (described as reduced irritability and improved activity). No patient presenting with seizures was identified, although they are a common sign of HPeV neuroinfection[1,7,8]. Most infants showed skin symptoms, but specific palmoplantar erythema, described as a diagnostic clue of HPeV infection[9], did not appear in any of the patients.

CSF data were consistent with the formerly described phenomenon of non-inflamed CSF in HPeV infections[1,5,7,8]. Normocytic anaemia and lymphopaenia, which usually accompany viral inflammation, were also reported. Additionally, abnormal liver enzymes and deranged coagulation profiles were identified, but none of the patients was diagnosed with neonatal hepatitis-coagulopathy syndrome related to HPeV[10]. It needs to be emphasised that the study group was small, so the results may vary from those previously reported.

The myelination process and neonatal brain maturation make the interpretation of MRI findings difficult. Therefore, other abnormalities in addition to the non-specific lesions already found cannot be excluded[11].

A severe course of HPeV infection mostly occurs in newborns and young infants; nevertheless, the epidemiology and pathogenesis remain unexplained[1]. Although no difference in sex distribution was observed in the previous studies[2], some reports, including this case series, noted a male predominance among HPeV sepsis-like cases[8]. The fact that infants are at a higher risk of developing a severe course of HPeV infection indicates that perinatal factors might influence the baby's protection against HPeVs[7]. Aizawa et al. found that infants born to older mothers were more susceptible to severe HPeV-related diseases[12]. In the reported study, the majority of the mothers were above 35 years old at delivery, which seems to support Aizawa's finding. Although the mode of delivery was not previously associated with the risk of HPeV infection, there was a higher rate of children with HPeV sepsis-like encephalitis born by vaginal route compared to those born by caesarean section. This observation could support the thesis about a weaker non-specific humoral response and, consequently, poorer control of viral infection in infants born by vaginal delivery[13]. In some studies, breastfeeding was shown to have a protective effect against enteroviruses[14], which are closely related to HPeVs; nevertheless, no such observation was made in this case series.

The fact that all the patients were second-borns, and the median age gap to the sibling was 2.5 years supports the hypothesis that having an older sibling (<3 years old) is a risk factor of contracting HPeV[2].

There are currently no antiviral drugs or vaccines against HPeVs[1]. Empirical treatment, consisting of ampicillin and gentamicin, had been administered to four patients until the aetiological agent was identified, following which the treatment was primarily supportive. Nowadays, the American Academy of Pediatrics highlights the urgent need to minimise antibiotic usage in perinatal medicine[15]; therefore, the importance of identification of non-bacterial causes of the disease is emphasised.

Although the diagnosis was confirmed relatively quickly, the patients were hospitalised for a long period because of the prolonged neurological presentation. Moreover, there is no approved specific antiviral or supportive therapy that could reduce recovery time and the length of hospitalisation.

Follow-up was initiated in all the infants described in this case series as part of an ongoing research project.

CONCLUSIONS

As the prevalence of HPeV encephalitis grows, the necessity to perform CSF PCR despite the lack of signs of inflammation in the CSF in patients presenting with sepsis-like illness is gaining relevance. Identification of the aetiological factor of infection is crucial to minimise antibiotic overuse in perinatal medicine, and ensure an appropriate diagnostic process and further follow-up of patients.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

DOI: 10.15557/PiMR.2023.0067

Acknowledgments

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.

Author contributions

Original concept of study: JŚ. Collection, recording and/or compilation of data: JŚ. Analysis and interpretation of data: JŚ. Writing of manuscript: JŚ. Critical review of manuscript: AP, EK. Final approval of manuscript: AP, EK.

Piśmiennictwo

1. Kadambari S, Harvala H, Simmonds P et al.: Strategies to improve detection and management of human parechovirus infection in young infants. Lancet Infect Dis 2019; 19: e51–e58.
2. Nielsen NM, Midgley SE, Nielsen AC et al.: Severe human parechovirus infections in infants and the role of older siblings. Am J Epidemiol 2016; 183: 664–670.
3. Diagnostic criteria for encephalitis and encephalopathy [Johns Hopkins website]. Last updated: 29 May 2016. Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540639/0/Encephalitis_Table_3.
4. National Institute for Health and Care Excellence: Sepsis: recognition, diagnosis and early management. NICE guideline [NG51]. Last updated: 13 September 2017. Available from: https://www.nice.org.uk/guidance/ng51.
5. Sharp J, Harrison CJ, Puckett K et al.: Characteristics of young infants in whom human parechovirus, enterovirus or neither were detected in cerebrospinal fluid during sepsis evaluations. Pediatr Infect Dis J 2013; 32: 213–216.
6. Children's Reference Ranges for FBC [NHS website]. Available from: https://www.nbt.nhs.uk/sites/default/files/Childrens%20FBC%20Reference%20Ranges.pdf.
7. Olijve L, Jennings L, Walls T: Human parechovirus: an increasingly recognized cause of sepsis-like illness in young infants. Clin Microbiol Rev 2017; 31: e00047-17.
8. Britton PN, Dale RC, Nissen MD et al.; PAEDS-ACE Investigators: Parechovirus encephalitis and neurodevelopmental outcomes. Pediatrics 2016; 137: e20152848.
9. Shoji K, Komuro H, Miyata I et al.: Dermatologic manifestations of human parechovirus type 3 infection in neonates and infants. Pediatr Infect Dis J 2013; 32: 233–236.
10. Levorson RE, Jantausch BA, Wiedermann BL et al.: Human parechovirus-3 infection: emerging pathogen in neonatal sepsis. Pediatr Infect Dis J 2009; 28: 545–547.
11. Soun JE, Liu MZ, Cauley KA et al.: Evaluation of neonatal brain myelination using the T1- and T2-weighted MRI ratio. J Magn Reson Imaging 2017; 46: 690–696.
12. Aizawa Y, Watanabe K, Oishi T et al.: Role of maternal antibodies in infants with severe diseases related to human parechovirus type 3. Emerg Infect Dis 2015; 21: 1966–1972.
13. Huurre A, Kalliomäki M, Rautava S et al.: Mode of delivery – effects on gut microbiota and humoral immunity. Neonatology 2008; 93: 236–240.
14. Sadeharju K, Knip M, Virtanen SM et al.; Finnish TRIGR Study Group: Maternal antibodies in breast milk protect the child from enterovirus infections. Pediatrics 2007; 119: 941–946.
15. Sola A: Abuse of antibiotics in perinatology: negative impact for health and the economy. Neoreviews 2020; 21: e559–e570.