

소아청소년기 중추신경 감염의 주요 원인으로서는 Human Parechovirus의 의의

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Human Parechovirus as an Important Cause of Central Nervous System Infection in Childhood

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Purpose: Human parechovirus (HPeV) is an increasingly recognized pathogenic cause of central nervous system (CNS) infection in neonates. However, HPeV infections have not been studied in older children. This study determined the prevalence and clinical features of HPeV CNS infection in children in Korea.

Methods: Reverse transcription polymerase chain reaction assays were performed using HPeV-specific, 5' untranslated, region-targeted primers to detect HPeV in cerebrospinal fluid (CSF) samples from children presenting with fever or neurologic symptoms from January 1, 2013, to July 31, 2014. HPeV genotyping was performed by sequencing the viral protein 3/1 region. Clinical and laboratory data were retrospectively abstracted from medical records and compared with those of enterovirus (EV)-positive patients from the same period.

Results: Of 102 CSF samples, six (5.9%) were positive for HPeV; two of 21 EV-positive samples were co-infected with HPeV. All samples were genotype HPeV3. Two HPeV-positive patients were <3 months of age and four others were over 1 year old. While HPeV-positive infants under 1 year of age presented with sepsis-like illness without definite neurologic abnormalities, HPeV-positive children over 1 year of age presented with fever and neurologic symptoms such as seizures, loss of consciousness, and gait disturbance. The CSF findings of HPeV-positive patients were mostly within the normal range, whereas most (73.7%) EV-positive patients had pleocytosis.

Conclusions: Although HPeV is typically associated with disease in young infants, the results of this study suggest that HPeV is an emerging pathogen of CNS infection with neurologic symptoms in older childhood.

Key Words: Parechovirus; Central nervous system infections; Korea

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Introduction

Human parechovirus (HPeV) was initially classified as echovirus 22 and echovirus 23 within the *Enterovirus* (EV) genus in the *Picornavirus* family¹; however, they were renamed and reclassified in HPeV genotypes 1 and 2 based on phylogenetic analysis in the 1990s^{2,3}.

Although over 16 HPeV genotypes have been identified⁴⁾, HPeV1 and HPeV3 are the most prevalent genotypes⁵⁾. HPeV genotypes other than HPeV3 most often present as mild respiratory or gastrointestinal disease, often at ages greater than 3 months⁶⁾. HPeV3 is the important cause of severe viral sepsis and central nervous system (CNS) infection in the infants less than the age of 3 months^{7,8)}. Seasonality and yearly variation have been reported for different HPeV genotypes and regions. Types causing sepsis-like illnesses and CNS infections in young infants have peaks from spring to autumn generally with a similar season as that of EVs^{9,10)}. The clinical presentations of HPeV3 CNS infection in young infant mimic those of other viral CNS infections such as EV¹¹⁾. However, very limited reports are available on the data of HPeV CNS infections in older children or adults¹²⁻¹⁴⁾.

To identify the characteristics of HPeV CNS infections in Korean childhood, we tested HPeV from cerebrospinal fluid (CSF) samples. We herein describe the epidemiologic, clinical and laboratory characteristics of HPeV CNS infection in Korean children.

Materials and Methods

1. Clinical specimens and data

Leftover CSF specimens were collected from patients who presented with fever or neurologic symptoms and underwent lumbar puncture at the Seoul National University Children's Hospital from January 2013 to July 2014 and were stored at -80°C . All the CSF samples were tested for common bacterial pathogens by routine microbiological methods. EV was tested on the CSF by GeneXpert EV assay (Cepheid, Sunnyvale, CA, USA) or reverse transcription polymerase chain reaction (RT-PCR) as part of standard of care for pediatric patients with fever or neurologic symptoms treated at Seoul National University Children's Hospital. Clinical and laboratory information were retrospectively collected from the medical records of the hospitalized patients for whom a positive PCR for HPeV was obtained. We compared the clinical and laboratory features in HPeV-

positive patients with those in EV-positive patients during the same time period. The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. H-1101-112-353).

2. Molecular characterization for HPeV

The viral RNA were extracted from CSF samples using QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. Synthesis of cDNA was carried out in a 30 μL reaction containing 17.5 μL RNA elution volume, 1 μL 150 ng/ μL random hexamers (Invitrogen, Carlsbad, CA, USA), 1 μL 10 mM deoxynucleotide triphosphate (dNTP), 6 μL 5 \times reaction buffer (Invitrogen), 3 μL 0.01 M dithiothreitol, 1 μL RNaseOUT (Invitrogen), and 0.5 μL 200 U/ μL Superscript II reverse transcriptase (Invitrogen), with incubation at 65°C for 5 minutes, on ice for at least 1 minute, 25°C for 5 minutes, 42°C for 90 minutes, and 70°C for 15 minutes.

To detect the HPeV-specific 5' untranslated region, RT-PCR assays were performed. PCR reaction included 2 μL cDNA template, 2 μL 10 \times PCR buffer (Takara, Shiga, Japan), 2 μL 25 mM MgCl_2 , 1.6 μL 2.5 mM dNTP, 0.4 μL 10 pM each primer as described previously²⁾, and 0.2 μL 5 U/ μL Taq DNA polymerase (Takara), in a total volume of 20 μL , with incubation at 95°C for 5 minutes prior to 35 amplification cycles (95°C for 30 seconds, 53.5°C for 40 seconds, and 72°C for 40 seconds), followed by 7 minutes at 72°C . A positive amplification HPeV control strain and negative control were included for quality control. HPeV positive control was provided by Dr. Ju-Young Chung's Lab, the Inje University Sanggye Paik Hospital, Seoul. For amplification of complete viral protein 3/1 (VP3/VP1) sequences from HPeV, nested RT-PCR assays were performed with the previously described primers¹⁵⁾ under the following reaction conditions: incubation at 95°C for 5 minutes prior to 45 cycles of 30 seconds at 95°C , 40 seconds at 45.3°C , and 40 seconds at 72°C , combined with a final extension of 7 minutes.

PCR products were purified and sequenced by Macrogen Korea Inc. (Seoul, Korea). The DNA sequence

analysis was done by using the nucleotide blast program (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>) to assess VP3/VP1 region for HPeV genotyping.

3. Statistical analysis

Analysis was performed using PASW version 18 (SPSS Inc., Chicago, IL, USA). Statistical analysis was analyzed for continuous variables using the t-test and for independent non-continuous variables using the chi-square test to compare HPeV infection and EV infection. A $P < 0.05$ was considered to be significant.

Results

1. Prevalence of HPeV in CSF samples

From January 2013 to July 2014, 102 CSF samples from the children <15 years of age were available for HPeV testing. Six children (5.9%) had positive test results for HPeV and 21 (20.6%) had positivity for EV in their CSF. Two CSF samples were positive for both HPeV and EV. HPeV-positive specimens were typed by sequencing the VP1 region and all of these were identified as HPeV3 sequences shared $\geq 93\%$ nucleotide identity.

2. Epidemiological findings of HPeV in Korean children

HPeV was detected on June in 2013 and from May to July in 2014. EV was mainly detected from late May to early August every year. The median age of HPeV-infected children was 33.5 months. Two HPeV-positive patients were <3 months of age, but the four others were over the age of 1 year (range, 19 to 180 months). For children infected with EV, median age was 2 months and range of age at diagnosis was 13 days to 7 years old (Table 1).

3. Clinical characteristics of children with positive-HPeV in CSF

All children with HPeV positivity were born at term. Except one patient who had Sturge-Weber syndrome, the majority of the HPeV-positive children have been healthy prior to the admission to the hospital. The

mean duration of hospital stay was 3.67 days. Fever was present in all children with HPeV infection, the mean duration of fever was 2.33 days. Mean values of hospital days, fever duration, and maximal body temperature did not differ between the HPeV-positive patients and the EV-positive patients.

Two infants under 3-month-old showed signs of sepsis-like illness such as fever or lethargy without definite neurologic abnormalities. Four children over 1-year-old presented definite neurologic symptoms, namely seizure, loss of consciousness, or gait disturbance (Table 2). Initial diagnosis prior to the detection of HPeV in the CSF includes meningitis in two patients

Table 1. Differences in Clinical and Laboratory Features in Patients with Human Parechovirus or Enterovirus

Variable	HPeV* (n=6)	EV† (n=19)	P-value
Age	33.5 mo (1 mo–15 yr)	2 mo (13 day–7 yr)	NS
Hospital days (day)	3.8 (1–11)	3.5 (1–6)	NS
Clinical symptoms			
Days of fever (day)	3.2 (2–4)	2.9 (1–5)	NS
Tmax hospital (°C)	38.8 (38–40.4)	38.7 (38.2–39.4)	NS
Neurologic symptoms (%)‡	66.7 (n=4)	5.3 (n=1)	0.001 [§]
Gastrointestinal symptoms (%)	66.7 (n=4)	47.4 (n=9)	0.001 [§]
Respiratory symptoms (%)	33.3 (n=2)	10.5 (n=2)	NS
Cerebrospinal fluid			
Pleocytosis (%)	16.7 (n=1)	73.7 (n=14)	0.001 [§]
Glucose level (mg/dL)	72.7 (64–95)	57.2 (45–74)	0.020 [§]
Protein level (mg/dL)	32.2 (15–67)	60.9 (19–116)	0.030 [§]
Blood			
WBC counts (/ μ L)	9,205 (7,680–23,740)	11,580 (6,280–15,140)	NS
Neutrophils (%)	61.2 (33.7–82.6)	60.5 (26.0–91.0)	NS
Lymphocytes (%)	29.0 (13.5–51.8)	29.1 (5.3–55.3)	NS
Platelet counts ($\times 10^3$ / μ L)	308.8 (238–364)	330.1 (187–516)	NS
C-reactive protein (mg/dL)	0.51 (0.09–7.64)	0.48 (0.03–2.72)	NS
AST (IU/L)	28.4 (16–47)	38.6 (17–81)	NS
ALT (IU/L)	16.4 (11–26)	23.5 (8–48)	NS

Values are presented as median (range).

*Two cerebrospinal fluid samples were positive for both HPeV and EV.

†Patients with EV not HPeV.

‡Neurologic symptoms except headache.

[§] $P < 0.05$.

^{||}Age-adjusted results.

Abbreviations: HPeV, human parechovirus; EV, enterovirus; NS, not significant; Tmax, maximum body temperature; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase.

Table 2. Characteristics of the Six Positive Human Parechovirus Cases

Patient	Age	Sex	Initial impression	Fever		Symptom	CSF			Peripheral blood					Brain MRI	HPeV genotyping	GXEA
				Duration (day)	Tmax (°C)		Cell counts (/mm ³)	Glucose (mg/dL)	Protein (mg/dL)	WBC counts (/μL)	Neut (%)	Lymph (%)	PLT counts (×10 ³ /μL)	CRP (mg/dL)			
1	6 yr	F	Febrile convulsion	2	40.4	Headache, seizure, abdominal pain, diarrhea, cough, coryza, sore throat	0	95	20	23,740	69.6	21.4	364	7.64	No specific findings	HPeV3	(+)
2	15 yr	M	Aseptic meningitis	4	38.9	Headache, loss of consciousness, vomiting	132	65	50	8,970	71.2	16.9	298	0.71	Slightly prominent meningeal enhancement	HPeV3	(+)
3	1 mo	M	Aseptic meningitis	1	38.2	Fever without focus	7	71	15	9,440	33.7	51.8	325	0.09	ND	HPeV3	(-)
4	19 mo	M	Acute cerebellar ataxia	11	38	Gait disturbance, vomiting, cough, coryza	3	74	23	7,680	68.8	20.1	238	2.19	No specific findings	HPeV3	(-)
5	3 mo	M	Sepsis	1	38.4	Lethargy	0	64	18	9,890	41.2	50.3	331	0.15	ND	HPeV3	(-)
6	4 yr	F	Common cold, known Sturge-Weber syndrome	4	38.6	Seizure aggravation, headache, vomiting	0	67	67	8,300	82.6	13.5	297	0.3	More prominent sulcal hyperintensity and leptomeningeal enhancement of temporo-occipital lobe (aggravated chronic ischemia suggested)	HPeV3	(-)

Abbreviations: Tmax, maximum body temperature; CSF, cerebrospinal fluid; WBC, white blood cell; Neut, neutrophil; Lymph, lymphocyte; PLT, platelet; CRP, C-reactive protein; MRI, magnetic resonance imaging; HPeV, human parechovirus; GXEA, GeneXpert enterovirus assay; ND, not done.

and neonatal sepsis, febrile convulsion, acute cerebellar ataxia each. One child with preexisting Sturge-Weber syndrome developed seizures. Aggravation of underlying chronic ischemia revealed on his brain magnetic resonance imaging (MRI). Seizure was presented in two children including patient with preexisting Sturge-Weber syndrome, and gait disturbance was noted for one child but his brain and spine MRI showed no specific abnormalities. Loss of consciousness was presented in one patient and his brain MRI suggested meningitis, but he was co-infected with EV meningitis. Neurologic imaging was performed on 4/6 (66.7%) of patients with HPeV infection during the acute phase of their illness. Two children under 1-year-old were excluded because they had no CNS-specific symptoms such as seizure, loss of consciousness, or gait disturbance. Other clinical symptoms were abdominal pain, diarrhea, vomiting, cough, coryza, or headache. Rashes were not noted. CNS-specific symptoms were much more common in children with HPeV (4/6, 66.7%) compared with those positive for EV (1/19, 5.3%).

The maximum cell counts of HPeV-positive CSF were 132 cells/mm³ but overall cell counts were within age-

adjusted normal range except one patient who had a co-infection of EV and HPeV. In comparison, 73.7% (14/19) of EV-positive patients had CSF pleocytosis above the age-adjusted normal range. Overall, glucose and protein levels of the HPeV-positive CSF were within normal range. Mean protein level of the CSF was significantly lower in the patients with HPeV (33.2 mg/dL) than those with EV (60.9 mg/dL) ($P=0.027$). Except one child with co-infection of EV and HPeV, peripheral white blood cell was within age-adjusted normal range in all children with CSF positivity of HPeV. Peripheral neutrophil or lymphocyte proportion, C-reactive protein (CRP), or liver function test results were within age appropriate normal range in both HPeV-positive and EV-positive children.

Discussion

HPeV3 is the one of currently emerging viral cause of infant CNS infection, and HPeV3 is the most frequent genotype¹⁶. Clinical manifestations of HPeV infections are diverse. While HPeV types other than HPeV3 often

cause less severe respiratory or gastrointestinal disease often in older children, HPeV3 infection presents as sepsis or meningitis mostly in young infants¹⁷⁾. However, available reports of HPeV CNS infections in older children or adults are very limited¹²⁻¹⁴⁾.

In this study, 102 CSF samples from January 2013 to July 2014 were investigated to analyze HPeV infection in this study from the children <3 months of age with fever or <15 years of age with neurologic symptoms and underwent lumbar puncture at Seoul National University Children's Hospital. Our results of an overall prevalence of HPeV of 5.9% in pediatric CSF samples are similar to the prevalence rates found in the prior reports including Korea^{6,18)}.

A striking finding of this study is the observation that HPeV was detected from childhood over 1-year-old not only infants and CNS-specific symptoms were significantly more common among older children compared with infants. Four out of six children (66.7%) with HPeV-positive CSF had neurologic symptoms such as seizure, loss of consciousness, or gait disturbance. CNS symptoms were dominant among older children over 1-year-old with HPeV positivity. Of the four children with HPeV infection who experienced neurologic symptoms, one patient had an underlying medical condition predisposing them to seizures and the other two patients were co-infected with EV and HPeV. HPeV is often co-infected with other viruses including EV in respiratory or gastrointestinal diseases^{15,19,20)}. However, available reports are very limited on the data of co-infections of EV with HPeV CNS infection²¹⁾. In this study, we found that HPeV were co-detected in CSF of two EV-infected children. They were over 6-year-old and also presented with CNS-specific symptoms such as seizure and loss of consciousness. These findings suggested that older children with HPeV CNS infection may be presented with the neurologic symptoms or co-infection with HPeV and EV may easily cause the neurologic symptoms in older children.

It is remarkable that nearly all children not just infants with HPeV-positive PCR on CSF had no pleocytosis (5/6; 83.3%), including one of the two who had a co-infection with EV. In contrast to this, pleocytosis was

more commonly found in EV-positive CSF samples (14/19, 73.7%). CSF glucose and protein levels are not definitely increased or decreased in HPeV-positive CSF samples. This confirms the findings of other recent studies^{16,18)}. It serves as an important information for clinicians to rule out CNS infection based on normal CSF findings, highlighting the clinical importance of HPeV.

There are diverse reports on laboratory features of peripheral blood with HPeV infection. Although leukopenia is more reported in the previous studies^{9,16,22)}, mildly increased or normal leukocyte blood counts are also reported in the other studies^{10,18,23)}. CRP or liver function test levels remains normal or slightly increased in HPeV infection^{6,11,16,24)}. In the other hands, leukocytosis or elevation of CRP or liver function test levels are more frequently seen with EV infection^{10,11,16,22)}. In this study, one 6-year-old girl with co-infection of EV and HPeV showed peripheral leukocytosis and CRP elevation, and the other five HPeV-infected children presented the normal levels of peripheral blood test. The laboratory features of peripheral blood did not significantly differ between the HPeV-positive patients and the EV-positive patients.

This study shows that the prevalence of HPeV CNS infection in children >1-year-old is probably largely underestimated when the diagnosis of viral infection is suspected but not proven. Although it was previously documented that HPeV are frequently detected in neonates with sepsis-like symptoms, our study reports a high HPeV prevalence in a cohort of unselected childhood patients from all age groups with a suspicion of viral infection. Further studies are needed to characterize clinical features of HPeV infection in children. As a large tertiary children's hospital and referral center, patients with simple or benign clinical features are underrepresented compared with patient cohorts from the community. We may be underestimating the real prevalence of HPeV as etiological factor in children with CNS infection especially under 1-year-old. The prior studies showed yearly or seasonal prevalence variation, and differences in seasonality have been reported for different HPeV genotypes or geographic

variation^{6,16,18}. The duration of our study is not enough to show the variation.

In conclusion, this study demonstrated that HPeV has been detected in CSF from young infants with sepsis-like presentation and older children with neurologic symptoms. Our results suggest that HPeV should be suspected and included in the work-up in children >1 years of age and not restricted to neonates. Further studies are needed to characterize clinical features of HPeV infection in children.

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요약

목적: Human parechovirus (HPeV)는 영아에서 중추신경계 감염 및 패혈증의 주요한 원인의 하나로 최근에 새로이 주목받고 있는 바이러스이다. 그러나, 영아 이후 시기에 발병하는 HPeV 감염에 대한 연구나 보고는 거의 없다. 본 연구는 소아기 전 연령대에 걸친 HPeV의 국내 유병률 및 그 임상적 특징을 알아보려고 하였다.

방법: 2013년 1월부터 2014년 7월까지 발열 혹은 수막염 의심 증상으로 서울대학교병원에 내원하여 뇌척수액 검사를 시행 받은 소아의, 보호자 서면 동의를 얻어 수집한 잉여 뇌척수액 검체를 대상으로 하였다. 뇌척수액 검체에서 HPeV 특이 5' untranslated region을 역전사 중합효소연쇄반응(reverse transcription polymerase chain reaction)으로 증폭하여 HPeV 감염을 진단하고, HPeV의 viral protein 3/1 (VP3/VP1) region의 염기서열을 분석하여 유전자형을 확인했다. 이들의 임상 및 진단검사적 특징을 후향적 의무기록분석을 통해 평가하고, 같은 시기에 뇌척수액 GeneXpert (Cepheid)검사로 진단된 장바이러스(enterovirus [EV]) 수막염 환자군과 비교하였다.

결과: 총 102개의 뇌척수액 검체를 분석하였다. 이 중 HPeV 양성인 검체는 6개(5.9%)였고, 21개의 EV 양성 검체 중 2개에서 HPeV가 함께 검출되었다. HPeV는 2013년 6월과 2014년 5월에서 7월 사이에 수집된 검체에서 나타났고, 모두 HPeV3형이었다. HPeV 양성인 환자 중 2명이 3개월 이하의 영아였고, 나머지 4명은 1세 이상이었다(19-180개월). 1세 이하의 HPeV 환자들은 특별한 신경학적 증상 없이 발열과 같은 비특이적 증상을 보였으나, 1세 이상의 HPeV 환자들에서는 발열과 함께 뇌전증, 의식 소실과 같은 중증 신경학적 증상이 동반되었다. EV 양성인 뇌척수액 검체의 대다수(73.7%)에서 뇌척수액 내 백혈구 증다증이 관찰된 반면, HPeV의 경우 연령 대비 정상 범위를 보였다.

결론: HPeV에 의한 중추신경 감염증은 주로 3개월 이하의 영아에서 호발하는 것으로 알려져 있으나, 본 연구에 의하면 영아기 이후의 소아청소년에서도 HPeV 감염이 발생할 수 있다. 특히, 영아기 이후의 소아청소년에서 신경학적 증상을 동반한 발열이 있으나 정상 뇌척수액 검사 소견을 보이는 경우 HPeV를 병원체의 하나로 고려할 필요가 있겠다. 국내 소아 전반에 있어서 HPeV 감염의 역학과 임상적 특징을 밝히기 위해 향후 추가 연구가 필요하다.