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

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Abstract

Background: Human parechovirus (HPeV) is an increasingly recognized pathogen as a cause of central nervous system (CNS) infection in neonates. However, HPeV infections have not been studied in older children beyond neonates. This study was performed to determine the prevalence of HPeV CNS infection and its clinical features in children from Korea.

Methods: Reverse transcriptase-polymerase chain reaction (RT-PCR) assays were performed using HPeV-specific 5' untranslated region (UTR)-targeted primers to detect HPeV in cerebrospinal fluid (CSF) samples of children who presented with fever or neurologic symptoms from January 1, 2013 to July 31, 2014. HPeV genotyping was performed by sequencing of the viral protein 3/1 (VP3/VP1) region. Clinical and laboratory data were abstracted from medical records retrospectively, and compared with those of enterovirus (EV)-positive patients from same period.

Results: Of 102 CSF samples, HPeV was positive in 6 (5.9 %) and co-detected in 2 of 21 EV-positive samples. All the samples were typed as HPeV3. Two HPeV-positive patients were <3 months of age, but four others were over the age of 1 year. While HPeV-positive infants under 1 year-old presented with sepsis-like illness without definite neurologic abnormalities, HPeV-positive children over 1-year-old presented with fever and neurologic symptoms such as seizure, loss of consciousness, or gait disturbance. CSF findings of HPeV-positive patients were mostly within the normal range whereas majority (73.7 %) of EV-positive patients had pleocytosis.

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

Background

Human parechovirus (HPeV) is an **increasingly recognized pathogen as a cause of central nervous system (CNS) infection in neonates.** However, HPeV infections have not been studied in older children beyond neonates. This study was performed to determine the prevalence of HPeV CNS infection and its clinical features in children from Korea.

Methods

-Seoul National University Children's Hospital in Korea, January 2013 to July 2014
-102 Cerebrospinal fluid (CSF) samples of children who presented with fever or neurologic symptoms
- HPeV detection: Reverse transcriptase-polymerase chain reaction (RT-PCR) assays using HPeV-specific 5' untranslated region (UTR)-targeted primers
-HPeV genotyping: sequencing of the viral protein 3/1 (VP3/VP1) region
-Retrospective medical records review

Results

-**HPeV (+) in 6 (5.9%) (Table 1)**
- ✓ **co-detected in 2 of 21 EV-positive samples**
- ✓ All the samples were typed as **HPeV3**
- ✓ **HPeV-positive children over 1-year-old (n=4)**
- ✓ While HPeV (+) infants under 1 year-old presented with sepsis-like illness without definite neurologic abnomalities, **HPeV (+) children over 1-year-old presented with fever and neurologic symptoms**.

-CSF findings of HPeV (+) patients were mostly within the normal range whereas majority (73.7%) of EV-positive patients had pleocytosis. **(Table 2)**

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**.

Table 1. Characteristics of the 6 Positive Human Parechovirus Cases

Patient	Age	Sex	Initial Impression	Fever		CSF				Peripheral Blood					HPeV Genotyping	GXEA
				Duration	Tmax (°C)	Symptoms	Cell counts (/mm³)	Glucose (mg/dl)	Protein (mg/dl)	WBC counts (/μl)	Neut (%)	Lymph (%)	PLT counts (x10³/μl)	CRP (mg/dl)	Brain MRI		
1	6 y	F	Febrile convulsion	2 d	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 y	M	Aseptic meningitis	4 d	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 m	M	Aseptic meningitis	1 d	38.2	Fever without focus	7	71	15	9,440	33.7	51.8	325	0.09	ND	HPeV3	(-)
4	19 m	M	Acute cerebellar ataxia	11 d	38	Gait disturbance, Vomiting, Cough, Coryza	3	74	23	7,680	68.8	20.1	238	2.19	No specific findings	HPeV3	(-)
5	3 m	M	Sepsis	1 d	38.4	Lethargy	0	64	18	9,890	41.2	50.3	331	0.15	ND	HPeV3	(-)
6	4 y	F	Common cold, Known Sturge-Weber syndrome	4 d	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	(-)

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; y.o., years old; m., months; d., days; F, female; M, male; ND, not done

Table 2. Differences in Clinical and Laboratory Features in Patients with Human Parechovirus or Enterovirus

		HPeV* (n=6)	EV† (n=19)	P value
Median Age (range)		33.5 m (1 m - 15 y)	2 m (13 d - 7 y)	NS
Hospital Days		3.8 d (1 d - 11 d)	3.5 d (1 d - 6 d)	NS
Clinical Symptoms	Days of Fever (range)	3.2 d (2 d– 4d)	2.9 d (1 d - 5 d)	NS
	Tmax hospital (range)	38.8°C (38 - 40.4°C)	38.7°C (38.2 – 39.4°C)	NS
	Neurologic symptoms‡	66.7 % (n=4)	5.3 % (n=1)	0.001Ⅱ
	Gastrointestinal symptoms	66.7 % (n=4)	47.4 % (n=9)	0.001Ⅱ
	Respiratory symptoms	33.3 % (n=2)	10.5 % (n=2)	NS
Cerebrospinal Fluid	Pleocytosis[ʃ]	16.7 % (n=1)	73.7 % (n=14)	0.001Ⅱ
	Glucose level (range)	72.7 mg/dL (64 - 95 mg/dL)	57.2 mg/dL (45 - 74 mg/dL)	0.02Ⅱ
	Protein level (range)	32.2 mg/dL (15 - 67 mg/dL)	60.90 mg/dL (19 - 116 mg/dL)	0.03Ⅱ
Blood	Median WBC counts (/μL)	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 (x10³/μL)	308.8 (238 - 364)	330.1 (187 - 516)	NS
	Median C-reactive protein	0.51 mg/dL (0.09 - 7.64 mg/dL)	0.48 mg/dL (0.03 - 2.72 mg/dL)	NS
	AST	28.4 IU/L (16 - 47 IU/L)	38.6 IU/L (17 - 81 IU/L)	NS
	ALT	16.4 IU/L (11 - 26 IU/L)	23.5 IU/L (8 - 48 IU/L)	NS

HPeV, human parechovirus; EV, enterovirus; Tmax, maximum body temperature; NS, non-significant; AST, aspartate aminotransferase glutamic-oxaloacetic transaminase; ALT, alanine aminotransferase.
*Two CSF samples were positive for both human parechovirus and enterovirus.
†Patients with enterovirus not human parechovirus.
‡Neurologic symptoms except headache.
ʃAge-adjusted results.
ⅡP value <0.05