영아에서 장바이러스 감염에 의한 수막염

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Enteroviral Meningitis in Infants

Purpose: Enteroviruses (EV) have been known as one of the important pathogens of aseptic meningitis in pediatrics. Clinical manifestations include asymptomatic cases to serious neurologic sequelae. This study aimed to describe an overview of the seasonality, laboratory, and clinical characteristics of enteroviral meningitis in pediatric patients over a 7-year period.

Methods: We performed a retrospective medical record review of patients with a positive cerebrospinal fluid (CSF) enterovirus polymerase chain reaction (PCR) result in the pediatric department of Chung-Ang University Hospital between January 2008 and December 2014. Patients were subsequently divided into ≤ 1 -year age group and > 1 -year age group.

Results: Of 302 patients with aseptic meningitis, 121 were diagnosed with enteroviral meningitis. There were 25 patients in the ≤ 1 -year age group. Patients were detected throughout all four seasons but were more prevalent in the summer months, especially July. Patients in the ≤ 1 -year age group had more seizures ($P=0.034$) and rashes ($P=0.001$), but fewer gastrointestinal symptoms ($P=0.001$) than patients in the > 1 -year age group. No significant difference was found between the two groups in terms of total white blood cell count and CSF analysis.

Conclusion: There is prominent summer seasonality for enteroviral meningitis detections. Seizures were more common in the ≤ 1 -year age group. The combination of information from epidemiologic, clinical, and laboratory findings are necessary to facilitate the diagnosis of enteroviral meningitis. Infants often do not exhibit the common signs of enteroviral meningitis, and are at an increased risk for seizure; therefore, physicians should pay particular attention to this population.

Key Words: Enteroviral meningitis, Infants, Seizures

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Introduction

Human enteroviruses (HEVs) are members of the Picornaviridae family, and have a single positive strand of ribo-nucleic acid (RNA). HEVs are classified into five species based on molecular and biological characteristics: HEV-A, HEV-B, HEV-C, HEV-D and poliovirus¹⁻³⁾. Members of the species HEV-A, HEV-B, HEV-C, and HEV-D are major human pathogens and are responsible for a wide spectrum of disease manifestations that vary with host serotype, age, and immune status⁴⁾. EVs are transmitted mostly by the fecal-oral route, but respiratory spread has also been reported⁴⁾. These pathogens cause various

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infections such as meningitis, encephalitis, gastroenteritis, myocarditis, pneumonia, sepsis, and hand-foot-mouth disease. They are neurotropic and potentially fatal with 10% of cases resulting in neurological sequelae particularly enterovirus 71, which has been associated with cases of severe neurological conditions, neurogenic pulmonary edema, and left ventricular failure. Enteroviruses present a major public health concern⁵⁻⁹. Especially for neonates and immunocompromised patients who are at greatest risk of developing fatal complications^{8,9}.

Among viral etiologies, more than 85% of the known causes of aseptic meningitis are due to HEVs^{10,11}. Neonates and infants are susceptible to enteroviral disease, which accounts for a large portion of febrile illness during the summer months^{4,12}.

This study aimed to describe an overview of the seasonality, laboratory, and clinical characteristics of enteroviral meningitis in pediatric patients over a 7-year period, with a particular focus on findings in infants.

Materials and Methods

1. Patients

A retrospective chart review was conducted in Chung-Ang University Hospital. The medical records of children less than 18 years of age hospitalized from January 2008 to December 2014 with a positive cerebrospinal fluid (CSF) enterovirus polymerase chain reaction (PCR) result were collected and reviewed. Demographic data, date of illness, clinical manifestations, and microbiological findings in CSF and blood samples were collected

from the laboratory database and admission records. CSF analysis included cell count, glucose, protein, culture, and PCR. The enterovirus PCR assay was performed using an in-house reverse transcription PCR (RT-PCR) method to analyze viral nucleic acid from CSF specimens.

2. Case definitions

Diagnosis of aseptic meningitis is made based on clinical manifestations, CSF pleocytosis and negative results of a bacterial culture and the latex particle agglutination test. Clinical manifestations of aseptic meningitis vary with the host's age. Children who can describe their symptoms report headache, vomiting, fever and neck stiffness while infants and neonates presented with nonspecific febrile illness such as irritability, vomiting, and poor oral intake. CSF pleocytosis is defined based on the patient's age: CSF white blood cell (WBC) count of >22 WBCs per mm³ in patients <4 weeks old, >15 WBCs per mm³ in patients 4-7 weeks old, and >5 WBCs per mm³ if the patient's age is ≥ 8 weeks¹³.

Multford and Graham's studies showed that infants may present with non-pleocytic viral meningitis; thus, we considered non-pleocytic CSF results to be aseptic meningitis in the current study^{4,15}.

Cases of EV meningitis were determined based on a positive CSF enterovirus RT-PCR result. Fever was defined as an axillary temperature $\geq 38^{\circ}\text{C}$. Gastrointestinal symptoms included nausea, vomiting, poor feeding, diarrhea, and abdominal pain. Non-enteroviral origins of meningitis occurring throughout the study period were excluded. Patients were subsequently divided into 2

Fig. 1. Distribution of enteroviral-positive patients ≤ 1 year of age from 2008 through 2014. Patients' ≤ 1 year of age diagnosed with enteroviral meningitis has been increasing.

groups; the first group included subjects ≤ 1 year old, and the second group included subjects who were >1 year old.

3. Statistical analysis

Statistical analyses were performed using PASW Statistics for Windows, Version 18.0. (SPSS, Inc., Chicago, IL, USA). Chi-squared tests were used to analyze categorical data. P-values <0.05 were considered statistically significant.

Results

A total of 302 specimens of cerebrospinal fluid were collected

Fig. 2. Mean age of enteroviral meningitis in each year from 2008 through 2014.

from patients under 18 years of age, who were diagnosed with aseptic meningitis. Among these, 121 were positive for enteroviral infections and they were included in the analysis. There were 25 patients in the ≤ 1 year age group and 96 patients in the >1 year age group. The incidence of enteroviral positive patients in the ≤ 1 year age group is reported from 2008 through 2014 in Fig. 1. The number of infants diagnosed with enteroviral meningitis has been increasing.

There were 8 patients with EV meningitis (38%) in 2008, 5 (10.6%) in 2009, 5 (13.5%) in 2010, 14 (51.8%) in 2011, 15 (34.9%) in 2012, 51 (66.2%) in 2013, and 23 (46%) in 2014. Infants accounted for 20.7% (25/121) of the patients. There were no infants in 2008 and 2009; however, there was 1 infant (20%) in 2010, 6 (42.9%) in 2011, 1 (6.7%) in 2012, 11 (21.6%) in 2013, and 6 (26%) in 2014. The mean ages of patients during the study period were: 7.8 years in 2008, 4.42 years in 2009, 5.20 years in 2010, 3.34 years in 2011, 6.2 years in 2012, 5.1 years in 2013, and 4.1 years in 2014 (Fig. 2).

New cases of EV meningitis were noted to occur during all four seasons. Patients were first detected as early as January and into late December (Fig. 3). However, the monthly distribution showed the highest prevalence in July.

The presenting manifestations in the ≤ 1 year age group were rash (3 patients, 12%), gastrointestinal symptoms, consisting of vomiting and lethargy (7 patients, 28%), seizure (4 patients, 16%), and fever (25 patients, 100%). Fever was the most common presenting symptom of EV meningitis among all patients (Table 1). Erythematous maculopapular rash on the trunks and extre-

Fig. 3. Monthly distribution of enteroviral meningitis cases from 2008 through 2014, showing incidence peaks in summer.

mities appeared more frequently in patients ≤ 1 year of age compared to patients older than 1 year ($P=0.001$). Gastrointestinal symptoms such as, nausea, vomiting, poor feeding, diarrhea, and abdominal pain appeared more often in patients >1 year of age ($P=0.001$). Seizures were present in 8 patients, one of whom developed complex febrile seizures. All seizures were accompanied by a fever. In terms of seizure type, subtle seizures with apneic attacks were observed in 3 patients, and generalized tonic clonic movements were observed in 5 patients. Each patient returned to a normal level of consciousness with stable vital signs following the end of the seizure. The youngest patient was 38 days old, 2 patients were 1 year old, and 5 patients were 2 years old. Significantly more seizures were noted in the group of patients ≤ 1 year old ($P=0.034$) compared to patients >1 year old. No morbidity and mortality were reported during the 7 years of the study period.

There were no significant differences between the two groups in total WBC count in the peripheral blood samples. The average number of WBCs in the peripheral blood of the ≤ 1 year age group and the >1 year age group was $11,868.8 \pm 6,198.9/\text{mm}^3$ and $10,667.4 \pm 3,703.0/\text{mm}^3$, respectively. However, peripheral blood findings in the ≤ 1 year age group included significantly higher aspartate transaminase (AST) and alanine transaminase (ALT) levels ($P=0.001$, $P=0.008$), and were lymphocyte dominant

Table 1. Clinical manifestations in 121 patients with enteroviral meningitis

Symptom and signs	≤ 1 year (n=25)	>1 year (n=96)	P^* -value
Rash	3 (12%)	0 (0%)	0.001
GI symptoms	7 (28%)	85 (88.5%)	0.001
Lethargy	1 (4%)	1 (1%)	0.301
Fever	25 (100%)	93 (96.8%)	0.371
Seizure	4 (16%)	4 (4.2%)	0.034

GI, Gastrointestinal.

* $P < 0.05$.

Table 2. Mean peripheral blood values of patients with enteroviral meningitis

Peripheral blood	≤ 1 year (n=25)	>1 year (n=96)	P^* -value
WBC ($/\text{mm}^3$)	$11,868.8 \pm 6,198.9$	$10,667.4 \pm 3,703.0$	0.362
Neutrophil (%)	45.9 ± 14.1	72.7 ± 15.4	0.001
Lymphocyte (%)	40.1 ± 15.2	20.5 ± 12.9	0.001
CRP (mg/L)	10.3 ± 11.4	8.5 ± 11.4	0.488
Platelet ($/\text{mm}^3$)	429.2 ± 114.1	290.1 ± 75.2	0.001
AST (IU/L)	46.0 ± 18.3	30.6 ± 16.6	0.001
ALT (IU/L)	35.0 ± 35.2	14.5 ± 6.6	0.008

WBC, white blood cell; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase.

* $P < 0.05$.

($P=0.001$) compared to the >1 year age group (Table 2). Similar to the peripheral blood findings, the WBC counts in the CSF did not differ significantly between the two age groups. Overall 64% (16/25) of patients in the ≤ 1 year age group and 45% (43/96) of patients in the >1 year age group revealed an absence of pleocytosis in the CSF analysis. CSF protein levels were higher in the ≤ 1 year age group, with an average of 72.9 ± 64.5 mg/dL ($P=0.013$) (Table 3).

Discussion

Previous studies have reported that EVs account for 63% of hospitalizations during the summer and fall, especially in infants less than 3 months of age¹⁶. Enteroviral meningitis has a strong seasonality and is most prevalent in May and July¹⁷⁻¹⁹. In our study, 121 cases of enteroviral meningitis were detected, with the highest prevalence in July. Such findings conform to those of previous studies. As Korea lies in a temperate region, a distinct seasonal pattern of enteroviral infection was noted.

The incidence of enteroviral meningitis during the outbreak seasons in Korea is an estimated 275 per 100,000 children, with a nationwide incidence of 3.48 per 1000 per year^{20,21}.

It occurs sporadically throughout the year in subtropical regions and in summer and fall in temperate regions.

Age distribution of patients with enteroviral meningitis among patients ≤ 1 year of age has been increasing. An increased occurrence of enteroviral meningitis in this population may be due to different viral serotypes, new genotype variants, environmental factors, and host immunity during epidemics. Immune systems of infants are not fully developed; they lack the ability to control infectious processes, resulting in a greater risk of serious infection from enteric viruses. Although in our study both patient groups were at risk of severe morbidity and mortality, they recovered without any severe complications. We presumed that these patients had not received higher viral

Table 3. Mean cerebrospinal fluid findings of patients with enteroviral meningitis

CSF Findings	≤ 1 year (n=25)	>1 year (n=96)	P^* -value
WBC ($/\text{mm}^3$)	111.7 ± 219.5	121.5 ± 216.7	0.841
Neutrophil (%)	16.3 ± 30.8	31.3 ± 34.7	0.04
Lymphocyte (%)	23.2 ± 37.4	35.1 ± 36.5	0.153
Protein (mg/dL)	72.9 ± 64.5	36.8 ± 63.5	0.013
Glucose (mg/dL)	60.7 ± 8.9	64.9 ± 10.1	0.068

CSF, cerebrospinal fluid; WBC, white blood cell.

* $P < 0.05$.

inoculums, but rather less virulent strains of enteroviruses. The

fact that enteroviruses have the potential to cause fatal complications, particularly enterovirus 71, which has been associated with cases of neurogenic pulmonary edema and left ventricular failure²²⁾. It is necessary to perform a study such as ours to know and expect the ranges of enteroviral disease.

Analysis of peripheral blood and CSF samples from both groups revealed that they were not definite indicators for enteroviral meningitis. Examinations of the CSF analysis revealed, the white blood cell counts were variable and, as seen in past studies, infants with enteroviral meningitis did not always demonstrate CSF pleocytosis^{15,23,24)}.

Our study had several limitations. First, this retrospective study of hospital records and CSF findings probably missed a significant number of clinically undiagnosed aseptic meningitis cases.

We did not perform serotype-specific EV identification; therefore, we could not identify new variations of different serotypes or changing epidemiology among infected younger infants. In addition, cases not covered by the laboratory's primers would lead to vast numbers of overlooked enteroviral meningitis cases. Second, the small study sample size increases the risk that our sample is not representative of the total pediatric population. This limits our ability to generalize our results regarding the seasonality, laboratory, and clinical characteristics of enteroviral meningitis to all children.

In conclusion, understanding the clinical spectrum of enteroviral meningitis presentation in infants is especially critical during epidemic seasons. It is important to consider meningitis even in the absence of its typical symptoms and CSF pleocytosis. The CSF findings were limited in terms of the differential diagnosis between bacterial and viral meningitis. Physicians should be aware that neurotropic enteroviral infections more often cause seizures in patients ≤ 1 year of age; thus, they should pay particular attention to this population. A well-designed prospective study is necessary for serotype-specific identification of enteroviral infections to observe changing epidemiology or new variations among pediatric patients. Furthermore, additional studies are necessary to find a reliable diagnostic test for infants with meningitis since CSF pleocytosis does not always occur. Since there are no definite criteria for diagnosing enteroviral meningitis, the combination information from epidemiologic, clinical and laboratory findings are necessary to facilitate the diagnosis of enteroviral meningitis. Infants often do not exhibit the common signs of enteroviral meningitis, and are at an increased risk for severe illness and complications; therefore, physicians should pay particular attention to this population.

요약

목적: 장바이러스는 소아의 무균성 수막염의 중요한 원인 중의 하나이다. 장바이러스 수막염은 다양한 임상 양상으로 발현되는데, 연령에 따라 무증상 감염부터 신경계 합병증까지 나타날 수 있다. 이 연구는 7년간 장바이러스 수막염으로 진단되어 치료받은 소아 환자들의 통해 역학 및 임상, 검사 결과의 특징을 비교 분석하고자 한다.

방법: 중앙대학교병원의 소아청소년과에서 2008년 1월1일부터 2014년 12월까지 7년동안 장바이러스 수막염으로 입원하여 치료받은 환자들의 의무 기록을 후향적으로 조사 하였다. 총 121명의 환자를 1세 미만의 그룹과 1세 이상의 그룹으로 나누어 임상적 특징, 혈액 검사 소견, 뇌척수액 소견을 비교 분석하였다.

결과: 전체 302명의 무균성 수막염 환자 중 121명이 장바이러스 수막염으로 진단받았다. 진단받은 전체 환자 121명 중 1세미만의 그룹은 25명이었고 계절별로는 여름에 발병률이 높았으며 특히 7월에 호발 하였다. 1세 미만의 그룹은 1세 이상 그룹과 비교 시 경련과 ($P=0.034$) 발진($P=0.001$) 통계적으로 유의하게 높았고 소화기계 증상은 유의하게 낮았다($P=0.001$). 검사소견상 혈액검사 및 뇌척수액의 백혈구 수는 두 그룹에서 모두 차이가 없었다.

결론: 장바이러스 수막염은 사계절 중 여름철에 호발하고 관련 합병증 중 신경학적 증상인 경련은 1세미만 영아에서 흔히 호발한다. 보다 빠른 진단을 위해서는 역학 및 임상, 검사실의 특징의 통합적인 자료가 필요하다. 장바이러스 수막염이 발병한 영아는 특징적인 소견이 없기에 의사들은 1세미만의 연령대에서 특히 주의를 기울여야 한다.

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