EMJ THE EWHA MEDICAL JOURNAL

Original Article

Ewha Med J 2017;40(3):122-127
https://doi.org/10.12771/emj.2017.40.3.122
eISSN 2234-2591

Clinical Characteristics and Epidemiology of Enteroviral Meningitis Compared to Non-Enteroviral Meningitis in Infants under 3 Months of Age

Jisoo Kim, Hee Won Kang, Young Min Youn, So-Yeon Shim, Eun Ae Park, Su Jin Cho

Department of Pediatrics, Ewha Womans University School of Medicine, Seoul, Korea

Objectives: To compare the epidemiology, clinical presentation, laboratory findings, seasonality and hospital course of enteroviral meningitis (EM) and non-enteroviral meningitis (NEM) cases in infants under 3 months of age.

Methods: A retrospective chart review was performed of infants under 3 months of age or less with viral meningitis admitted to Ewha Womans University Mokdong Hospital between January 2010 and December 2016.

Results: EM patients were more likely to have siblings compared with NEM. Most of EM was diagnosed during the summer season. Almost 80% of EM was diagnosed between July and September. Fever lasted longer in EM patients compared to NEM. White blood cell count (WBC) from the cerebrospinal fluid was higher in EM patients compared with NEM patients. WBC in blood were lower in EM patients compared with NEM patients. C-reactive protein was lower in EM patients compared with NEM patients. Most of the patients were initially started on antibiotics therapy to rule out bacterial meningitis. EM patients received shorter duration of antibiotic treatment compared with NEM patients.

Conclusion: This study was conducted to augment the understanding of the incidence, epidemiology, transmission in infants, clinical presentation, laboratory findings, seasonality and hospital courses of enteroviral meningitis compared to NEM. Early recognition, rapid diagnosis and proper clinical management can reduce duration of antibiotic treatment. **(Ewha Med J 2017;40(3):122-127)**

Received June 14, 2017
Revised July 5, 2017
Accepted July 6, 2017

Corresponding author
Su Jin Cho
Department of Pediatrics, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
Tel: 82-2-2650-2859, Fax: 82-2-2653-3718
E-mail: sujin-cho@ewha.ac.kr

Key Words
Enterovirus; Meningitis; Infant; Cerebrospinal fluid; Polymerase chain reaction

Introduction

Enterovirus is the predominant pathogen in children with aseptic meningitis [1]. In 80% to 90% of cases of viral meningitis are caused by nonpolio enteroviruses [1]. Nonpolio enterovirus infections are common in the preterm infants and newborns [2]. Enterovirus infections manifests with fever, lethargy, irritability and poor feeding with/without skin rash [2]. Most of the enteroviral meningitis (EM) is considered as asymptomatic or self-limiting disease with a good prognosis [3] and require only supportive management in older children [4]. Nonetheless, neonatal enterovirus infections manifest from asymptomatic to fatal [5]. These infections can cause sepsis, pneumonia, myocarditis, and multi-organ failure [2]. Severe forms include meningoencephalitis and hepatic necrosis with coagulopathy [5]. In approximately 10% of complicated cases have been reported including complex seizures, increased intracranial pressure, and coma [3]. In several studies of neonatal enterovirus infections, fatality rates were reported from 0% to 42% [5].

This study was conducted to augment understanding of the

incidence, epidemiology, transmission in infants, clinical presentation, laboratory findings, seasonality and hospital course of EM and non-enteroviral meningitis (NEM) in infants less than three months of age. Improved knowledge would be important for the optimal management of EM in this high-risk group.

Current literature describes that enterovirus infections following vertical transmission in neonates in the first days of life can cause high mortality and morbidity [6]. Infections after the first week of life have a more benign course and very low mortality rates [6]. Early recognition of potentially fatal enterovirus infection, and aggressive management at an early stage of diagnosis reduce mortality rates [5]. Also, rapid diagnosis and proper clinical management can reduce the cost of healthcare.

Methods

1. Datasets

A retrospective chart review was performed of infants under 3 months of age or less with viral meningitis admitted to Ewha Womans University Mokdong Hospital between January 2010 and December 2016.

2. Study definitions

EM was defined as having a positive result for enteroviral reverse transcription-polymerase chain reaction (RT-PCR) in cerebrospinal fluid (CSF) samples. NEM was defined as the group of the patients with non-enteroviral meningitis; pleocytosis in CSF under 3 months of age or less, without a specific virus nor bacteria identified.

In this study, pleocytosis was defined for neonates as a white cell count of >30 cells/mm^3 in CSF, for infants aged 1 to 2 months as a white cell count of >15 cells/mm^3 in CSF, and for infants aged 2 to 3 months as a white cell count of >5 cells/mm^3 in CSF.

Enterovirus screening was performed in the microbiology laboratory at Ewha Womans University Mokdong Hospital using commercial molecular diagnostic methods (Xpert EV; Cepheid, San Diego, CA, USA). The Cepheid Xpert EV assay is a RT-PCR technique [7]. The Cepheid Xpert EV assay carry out the assay of qualitative detection of enterovirus ribonucleic acid in cerebrospinal fluid specimens [7].

3. Statistical analysis

A descriptive analysis was performed. Expressing qualitative variables as proportions and quantitative variables as mean and standard deviation or median and interquartile range when appropriate. IBM SPSS ver. 19.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Statistical comparisons between the two groups were performed using the Fisher exact test and Pearson chi-square. In addition, nonparametric Mann-Whitney U test was used to compare the two groups with respect to clinical symptoms. A difference with P-value <0.05 was considered to be significant.

Results

1. Incidence and epidemiology

In this study, 249 infants were included. One hundred sixty-eight were positive for enterovirus (67.4%) and 81 were negative for enterovirus (32.5%). Mean age of EM patients was 42.46±28.43 days and that of NEM was 49.95±31.55 days (P=0.061). The male to female ratio for EM patients was 1.79:1, and the ratio for NEM patients was 1.07:1. The distribution of sex showed marginal differences (P=0.065). The mean birth weight was 3,209.6±547.43 g in EM patients, and 3,235.2±551.10 g in NEM patients (P=0.545). The mean gestational age was 38.67±1.86 weeks in EM patients, and 38.73±1.79 weeks in NEM patients (P=0.877). Out of 168 EM patients, 135 had siblings. Out of 81 NEM patients, 35 had siblings. EM patients were more likely to have siblings (80.4%) compared with NEM (43.2%; P< 0.001). Before the patients was admitted to the hospital, 26 EM patients used the postnatal care center (15.5%) and 6 NEM patients used the postnatal care center (7.4%; P=0.075) (Table 1).

2. Influence of seasonal variation

EM was diagnosed with a preponderance during the summer season. One hundred thirty-one infants (77.9%) were diagnosed with EM between July and September. Thirty-two patients (39.5%) of NEM was detected between July and September (Fig. 1).

3. Clinical features

Not all cases presented with fever. Out of 168 EM patients, 163 had fever (97.0%). Only 5 EM infants were afebrile. Out

Table 1. Epidemiology and clinical manifestations of enteroviral meningitis compared to non-enteroviral meningitis

Clinical feature	Enteroviral meningitis	Non-enteroviral meningitis	P-value
Male sex	87 (51.8)	52 (64.2)	0.065
Age (day)	42.46±28.43	49.95±31.55	0.061
Gestational age (wk)	38.67±1.86	38.73±1.79	0.877
Birth weight (kg)	3.20±0.54	3.23±0.55	0.545
Postnatal care center	26 (15.5)	6 (7.4)	0.075
Having siblings	135 (80.4)	35 (43.2)	<0.001
Temperature>37.9°C	163 (97.0)	69 (85.2)	0.001
Highest temperature (°C)	38.61±0.45	38.54±0.58	0.099
Fever duration (hr)	49.99±35.05	37.43±45.61	<0.001
Cough	28 (16.7)	21 (25.9)	0.085
Coryza	29 (17.3)	19 (23.5)	0.246
Vomiting	20 (11.9)	10 (12.3)	0.920
Diarrhea	32 (19.0)	11 (13.6)	0.285
Poor oral intake	28 (16.7)	9 (11.1)	0.248
Lethargy	4 (2.4)	4 (4.9)	0.280
Irritability	28 (16.7)	8 (9.9)	0.153
Jaundice	12 (7.1)	1 (1.2)	0.066
Skin rash	30 (17.9)	7 (8.6)	0.055
Oral ulcer	12 (7.1)	8 (9.9)	0.457
Convulsion	2 (1.2)	0	1.000

Values are presented as number (%) or mean±standard deviation.
Statistical significance level, P<0.05.

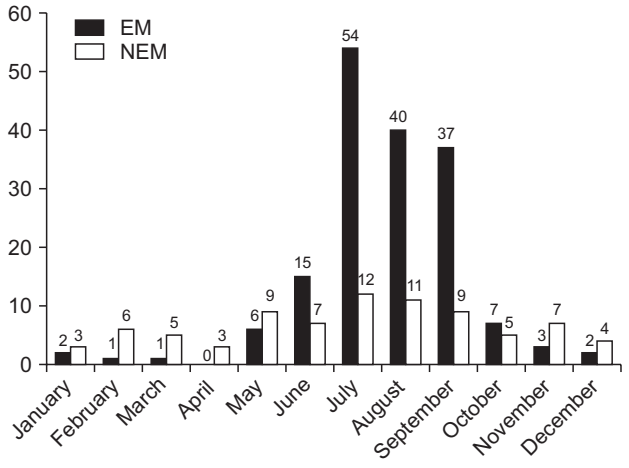

Fig. 1. The distribution by month of the enterovirus meningitis (EM) and non-enteroviral meningitis (NEM). EM incidences are shown in Fig. 1. The black bar is for EM patients, and the white bar is for NEM patients. EM has a summer seasonality compare with NEM.

of 81 NEM patients, 69 had fever (85.2%; P<0.001). Highest temperature of EM patients was 38.61°C±0.45°C and that of NEM patients was 38.54°C±0.58°C (P=0.099). Fever lasted for a mean of 49.99±35.05 hours in EM patients, and lasted a mean of 37.43±45.61 hours in NEM patients (P<0.001) (Table 1).

4. Laboratory data

Among the EM patients, 74 EM patients (44.0%) had CSF pleocytosis and 94 EM patients (55.9%) did not have CSF pleocytosis. WBC from the CSF sample was 151.52±586.93 cells/uL (range, 0–7,200 cells/uL) in EM patients, and 109.53 ±392.93 cells/uL (range, 5–2,996 cells/uL) in NEM patients (P=0.004). WBC in blood were 10.84±4.12×10^9/L in EM patients, and 15.15±6.49×10^9/L in NEM patients (P<0.001) (Table 2).

Serum aspartate aminotransferase was 54.78±59.84 IU/L in EM

Table 2. Laboratory findings, treatment of enteroviral meningitis compared to non-enteroviral meningitis

Clinical feature	Enteroviral meningitis	Non-enteroviral meningitis	P-value
CSF white blood cell (/mm^3)	151.52±586.93	109.53±392.93	0.004
CSF neutrophil (%)	16.19±26.96	16.18±27.10	0.717
CSF lymphocyte (%)	13.67±22.00	25.70±31.28	0.002
CSF monocyte (%)	16.19±25.53	25.71±26.75	0.001
CSF proteins (mg/dL)	68.50±53.57	85.93±80.45	0.114
CSF glucose (mg/dL)	51.58±8.94	51.53±11.67	0.488
Blood white blood cell (/mm^3)	10,847.86±4,127.13	15,155.06±6,491.64	<0.001
Blood neutrophil (%)	42.64±20.07	41.36±19.25	0.635
Blood lymphocyte (%)	44.96±19.42	44.25±18.05	0.784
Blood monocyte (%)	9.76±4.21	11.93±5.29	0.002
Serum aspartate aminotransferase (IU/L)	54.78±59.84	61.53±98.77	0.917
Serum alanine transaminase (IU/L)	34.44±56.16	46.15±130.99	0.819
Serum C-reactive protein (mg/L)	0.67±1.20	1.38±2.21	0.027
Antibiotic treatment (day)	5.03±4.22	5.84±3.87	0.034
Hospital stays (day)	7.06±8.79	6.78±4.01	0.536

Values are presented as mean±standard deviation.
CSF, cerebrospinal fluid.
Statistical significance level, P<0.05.

patients, and 61.53±98.77 IU/L in NEM patients (P=0.917). Serum alanine transaminase was 34.44±56.16 IU/L in EM patients, and 49.15±130.99 IU/L in NEM patients (P=0.819). C-reactive protein was 0.67±1.20 in EM patients, and 1.38±2.21 in NEM patients (P=0.027) (Table 2).

Four of EM patients had positive result from blood culture. Methicillin susceptible *Staphylococcus epidermidis*, methicillin resistant coagulase negative *S. epidermidis*, Clindamycin resistant *S. epidermidis*, and methicillin susceptible *S. parasanguinis* were cultured from the peripheral blood. None of NEM had positive result from blood culture.

5. Treatment

None of the infants were on antibiotics prior to admission. Most of the patients was started on antibiotics therapy after laboratory evaluations; blood culture and CSF culture. Most of patients received antibiotics until the bacterial etiology could be ruled out. Only 8 EM patients were not given antibiotics. When enterovirus was found in the CSF, pediatricians discontinued the antibiotics. EM patients received antibiotic treatment about 5.03±4.22 days, and NEM patients received antibiotic treatment about 5.84±3.87 days (P=0.034).

6. Hospitalizations and neurological sequelae

The duration of hospital stay was 7.06±8.79 days for EM and 6.78±4.01 days for NEM (P=0.245). None of EM or NEM patients were admitted to the neonatal intensive care unit. None of them needed mechanical ventilator support. None of them was diagnosed with enteroviral meningoencephalitis. Two of EM had seizures and one of them was prescribed oral phenobarbital. All EM and NEM patients were free of multisystem diseases. All EM and NEM patients were free of neurologic sequelae upon follow-up.

Discussion

We present a retrospective single center study at Ewha Womans University Mokdong Hospital of infants up to 3 months of age with EM or NEM. This may be a single center study but we were able to review all respective inpatient cases at Ewha Womans University Mokdong Hospital for the duration of 7 years.

EM was diagnosed with a preponderance during the summer season. Nonpolio enteroviruses are important pathogens in the neonatal period and account for a significant portion of febrile illness requiring hospitalization in infancy, particularly during

the summer months [8]. In the Canadian study of children, 802 cases of aseptic meningitis were collected over a 2-year period [1]. In that study, most of the proven EM and clinically aseptic meningitis occurred from July to October with sporadic cases in other months [1]. In this study, 131 EM patients were diagnosed with a preponderance during the summer season. 77.9% of the EM was diagnosed between July and September (Fig. 1). Predominantly the summer season, it is important to distinguish from enteroviral infections to non-enteroviral infections [9]. Early recognition, rapid diagnosis and proper clinical management can reduce mortality rates and decreased the duration of antibiotic treatment.

Enteroviruses are present in feces, urine, and respiratory secretions of infected individuals [6]. The transmission of enterovirus after birth appears to be via fecal to oral or respiratory routes [10]. When infection occurs within the 7 days of birth, it seems to be the result of vertical transmission [6]. The most common route of transmission of enterovirus is from mother to infant [11]. The nursery outbreaks also have been reported numerously [11]. The transmission of enterovirus after birth from siblings or father is relatively common [12].

In this study, 26 EM patients stayed at the postnatal care center and 6 NEM patients stayed at the postnatal care center before admission (P=0.075). In the postnatal care center, there are many neonates of similar ages. In the neonatal unit or postnatal care center, transmission of the virus from parents, older sibling, or infected staffs to other newborns is possible. Transmitting the virus is also possible from neonate to neonate in the neonatal unit or postnatal care center. Applying strict infection control can prevent the outbreak [6]. Early recognition and rapid diagnosis are very important to prevent the outbreak. Presence of a sibling, absence of CSF pleocytosis and elevated liver enzymes should prompt the clinician to recognize this common viral infection in a timely matter and test for enterovirus while monitoring for multisystem involvement.

Syriopoulou et al. [6] reported that enterovirus RT-PCR is an important means for early diagnosis of enterovirus infection [6]. Its sensitivity range is from 77% to 100% and its specificity range is from 83% to 97% [6]. Enterovirus RT-PCR is more sensitive than viral cultures [6]. Osterback et al. [13] reported that the patients with a positive result for enterovirus RT-PCR in CSF also had a positive result in the pharyngeal swab samples and fecal samples. Enteroviruses are secreted for a long period in feces and in pharyngeal samples [13]. Therefore the detection of enterovirus in feces or pharyngeal samples does not mean that it is the cause of meningitis [13]. A positive result for enterovirus RT-PCR in serum sample would be more causative, but only in a half of the meningitis cases had positive result for enterovirus RT-PCR in serum [13]. Thus, positive result for enterovirus RT-PCR in CSF sample cannot be replaced by others. In conclusion, enterovirus RT-PCR is an important means for early diagnosis of enterovirus infection [6].

Enterovirus PCR test from CSF sample is recommended to prevent unnecessary antibiotic use and prolonged hospitalization. In this study, most of the patients initially was started antibiotics therapy. Most of patients received antibiotics until the bacterial etiology could be ruled out. Only 8 EM patients were not given antibiotics in this study with prompt reporting of the RT-PCR results. When enterovirus was found in infants' CSF, pediatricians discontinued the antibiotics. EM patients received shorter duration of antibiotic treatment than NEM patients (P=0.034). Certain antibiotics carry risks and could increase the antibiotic-associated diarrhea [3]. Early laboratory confirmation of enteroviral infection could change management, reducing the period of unnecessary exposure to empirical antimicrobials uses, and permitting earlier discharge [14]. Positive result from enteroviral RT-PCR test allows to discontinue the antibiotics and shortens the length of hospital admission [4]. Above all, early recognition reduce mortality rates [5]. Early recognition via prompt enteroviral PCR testing of enterovirus enables the healthcare team members to prevent control spread of infection and to prevent the outbreaks. Hence is important [3].

This study has several limitations. There was no analysis about CSF pleocytosis along with age. There was no analysis about annual trend in comparison with the national epidemiological data. When we define the meaning of NEM, there was no consideration that partially treated bacterial meningitis, tuberculous meningitis, fungal meningitis or drug induced meningeal inflammation. Larger studies would help define the long-term prognosis for this two groups.

References

1. Lee BE, Chawla R, Langley JM, Forgie SE, Al-Hosni M, Baerg K, et al. *Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of aseptic meningitis. BMC Infect Dis*

2006;6:68.
2. Piralla A, Mariani B, Stronati M, Marone P, Baldanti F. *Human enterovirus and parechovirus infections in newborns with sepsis-like illness and neurological disorders. Early Hum Dev* 2014;90 Suppl 1:S75-S77.
3. March B, Eastwood K, Wright IM, Tilbrook L, Durrheim DN. *Epidemiology of enteroviral meningoencephalitis in neonates and young infants. J Paediatr Child Health* 2014;50:216-220.
4. Martin NG, Iro MA, Sadarangani M, Goldacre R, Pollard AJ, Goldacre MJ. *Hospital admissions for viral meningitis in children in England over five decades: a population-based observational study. Lancet Infect Dis* 2016;16:1279-1287.
5. Lin TY, Kao HT, Hsieh SH, Huang YC, Chiu CH, Chou YH, et al. *Neonatal enterovirus infections: emphasis on risk factors of severe and fatal infections. Pediatr Infect Dis J* 2003;22:889-894.
6. Syriopoulou VP, Hadjichristodoulou Ch, Daikos GL, Pirounaki M, Chatzicou V, Pavlopoulou I, et al. *Clinical and epidemiological aspects of an enterovirus outbreak in a neonatal unit. J Hosp Infect* 2002;51:275-280.
7. Alonso Perez N, Sagastizabal Cardelus B, Prieto Tato LM, Guillen Martin S, Gonzalez Torralba A, Garcia Bermejo I, et al. *Evaluation of an Xpert EV (Cepheid®) molecular diagnostic technique for enteroviral meningitis. An Pediatr (Barc)* 2016 Dec 2 [Epub]. https://doi.org/10.1016/j.anpedi.2016.09.010.
8. Hawkes MT, Vaudry W. *Nonpolio enterovirus infection in the neonate and young infant. Paediatr Child Health* 2005;10:383-388.
9. Groneck P, Jahn P, Schuler-Luttmann S, Beyrer K. *Neonatal enterovirus meningitis: transmission via parents during rooming-in and current epidemiology in Germany. Z Geburtshilfe Neonatol* 2011;215:1-5.
10. Gelber SE, Ratner AJ. *Hospital-acquired viral pathogens in the neonatal intensive care unit. Semin Perinatol* 2002;26:346-356.
11. Sawyer MH. *Enterovirus infections: diagnosis and treatment. Curr Opin Pediatr* 2001;13:65-69.
12. Tebruegge M, Curtis N. *Enterovirus infections in neonates. Semin Fetal Neonatal Med* 2009;14:222-227.
13. Osterback R, Kalliokoski T, Lahdesmaki T, Peltola V, Ruuskanen O, Waris M. *Echovirus* 30 meningitis epidemic followed by an outbreak-specific RT-qPCR. J Clin Virol 2015;69:7-11.
14. March B, Eastwood K, Wright IM, Tilbrook L, Durrheim DN. *Epidemiology of enteroviral meningoencephalitis in neonates and young infants. J Paediatr Child Health* 2014;50:216-220.