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Clinical characterization of benign enterovirus infection in neonates

Wenwen Chen, MD, Shuzhen Dai, MD, Liping Xu, MD*

Abstract

Enteroviruses is a group of positive single-stranded RNA viruses ubiquitous in the environment, which is a causative agent of epidemic diseases in children and infants. But data on neonates are still limited. The present study aimed to describe the clinical characteristics of enterovirus infection in neonates and arise the awareness of this disease to general public.

Between March 2018 and September 2019, data from all of the neonates diagnosed with enterovirus infection were collected and analyzed from neonatal intensive care unit of Zhangzhou Hospital in Fujian, China.

A total of 23 neonates were enrolled. All of them presented with fever (100%), and some with rashes (39.1%). The incidence of aseptic meningitis was high (91.3%), but only a small proportion (28.6%) presented with cerebrospinal fluid (CSF) leukocytosis. The positive value for nucleic acid detection in CSF was significantly higher than throat swab (91.3% vs 43.5%, $P = .007$). Five of the infected neonates presented with aseptic meningitis (23.8%) underwent brain magnetic resonance imaging examination and no craniocerebral injuries were found. Subsequent follow-ups were performed in 15 of them (71.4%) and no neurological sequelae was found.

Aseptic meningitis is a common type of enterovirus infection in neonates with a benign course. Nucleic acid detection of CSF has an important diagnostic value. Febrile neonates would be suggested to screen for enterovirus infection in addition to complete septic workup. An unnecessary initiation or earlier cessation of antibiotics could be considered in enterovirus infection, but that indications still need further studies to guarantee the safety.

Abbreviations: CA-16 = Coxsackie virus A16, CRP = C-reactive protein, CSF = cerebrospinal fluid, EV = enterovirus, EV-71 = enterovirus 71, IQR = interquartile range, PCT = procalcitonin, WBC = blood white blood cell.

Keywords: cerebrospinal fluid, enterovirus, meningitis, neonates, neurodevelopmental outcome

1. Introduction

The human enterovirus is a group of positive single-stranded RNA viruses which belong to the genus *Enterovirus* in the family *Picornaviridae*, exhibiting a surprising diversity of both genome sequences and genome layouts.[1,2] They are mainly divided into 4 species (enterovirus [EV]-A, EV-B, EV-C, and EV-D) based on the viral genetic characteristics. The best known members are the polioviruses, coxsackieviruses A and B, and echoviruses.[2,3] In addition, newly emerging EVs have been recognized and simply named EV followed by numbers sequentially.[4] EVs are associated with infectious disease with a diversity of clinical features from self-limited diseases to multiple organ dysfunction syndrome.[5]

Generally, EV infection can cause highly contagious disease in children 6?years old or younger.[6] Neonates with EV infection were formerly ignored because they were less frequently exposed to EV until they got older.[7] However, the absence of neutralizing antibodies makes the neonates vulnerable to EV infection.[8] In recent years, neonatal EV infection has been brought to attention since outbreaks of nosocomial infections in the newborn room have been reported frequently.[9,10] Neonatal EV infection which mimicked bacterial sepsis can cause serious complications such as myocarditis, meningoencephalitis, acute liver failure, or even death.[11,12] Previous studies revealed that EV infection accounted for about 15% to 40% of the etiology in febrile neonates admitted to hospital,[13,14] and aseptic meningitis is a common clinical type of infection.[15]

Hence, an awareness of the clinical characterization of EV infection in neonates may help neonatologists in diagnosing this disease timely. In this study, we described the clinical manifestations, laboratory tests, imaging findings, and short-term outcome of neonatal EV infection in detail and tried to find meaningful index to guide for the clinical management of this condition.

2. Material and methods

2.1. Study design

This is a single-center, retrospective study of EV infections performed at neonatal intensive care unit of Zhangzhou Hospital, a tertiary care center in Fujian province in China, from March 2018 to September 2019. Neonates with positive EV

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Department of Neonatology, Zhangzhou Hospital, Zhangzhou, Fujian, China.

** Correspondence: Liping Xu, Department of Neonatology, Zhangzhou Hospital, 59 Shenglixi Street, Zhangzhou, Fujian 363000, China (e-mail: zzsyxlp@163.com).*

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nucleic acid in throat swab or cerebrospinal fluid (CSF) samples were enrolled and their clinical records were analyzed. Details included contact history, demographic characteristics, clinical symptoms, laboratory tests, therapies, length of hospital stay, imaging, and outcomes. Laboratory tests included complete blood count, C-reactive protein (CRP), procalcitonin (PCT), blood bacterial culture, CSF routine and biochemical tests, CSF bacterial culture, EV nucleic acid of throat swab, and CSF samples. The detection of EV nucleic acid included universal sequence identification and genotypes distinction of Coxsackie virus A16 (CA-16) and EV-71 by reverse transcription polymerase chain reaction.

Neurodevelopmental assessment was designed for infants with aseptic meningitis after discharge at 3-, 6-, 12-, 18-, and 24-month age. The content consisted of physical examination at every follow-up and evaluation with the use of Gesell developmental schedules at 6-, 12-, and 24-month age. As for infants who did not come back for follow-up, we tried to find out about their situation by phone call.

The project was approved by Ethics Committee of Zhangzhou Hospital (2020LWB048).

2.2. Sample size estimation

Formula for comparison of means of sample and population, means between 2 samples, correlation coefficient of 2 indicators, and comparison of rates between 2 samples were used in sample size calculation with $\alpha = 0.05$, $\beta = 0.10$ for 2-tailed test. The mean duration of empirical antimicrobial therapy (48–72 hours), or traditional bacterial meningitis therapy (14 days), and the detectable rate of nucleic acid in CSF (85%) were learned from literatures.[16–18] The detectable rate of nucleic acid in throat swab was estimated to be 50%. The allowable error and standard deviation of the sample were set to be 2. The correlation coefficient was set to be 0.85. After calculation, the theoretical sample size should be 10 for analysis of correlation coefficient, 12 for comparison of rates between 2 samples, 21 for comparison of means of sample and population, and 42 for comparison of means between 2 samples. The retrospective nature of the study predetermines the actual sample size.

2.3. Definitions

EV infection was defined as positive EV nucleic acid in either throat swab or CSF or both, but negative bacterial cultures in blood and CSF. Aseptic meningitis was defined as positive EV nucleic acid in CSF, but negative in blood and CSF cultures. Blood white blood cell count (WBC) elevation was defined as $>12 \times 10^9$ cells/L. Serum CRP elevation was defined as >10 mg/L. PCT elevation was defined as >0.5 mg/L. CSF WBC elevation was defined as $>20 \times 10^6$ cells/L. CSF protein elevation was defined as >1.7 g/L. CSF glucose decline was defined as <400 mg/L.

2.4. Statistical analysis

Data were analyzed with the use of SPSS version 26 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as means ± standard deviation or medians with interquartile ranges (IQR) for continuous variables, and numbers (percentages) for categorical variables. Mann–Whitney rank sum test were used to compare continuous variables, whereas Kappa test or McNemar test were used to compare categorical variables between groups. Pearson correlation coefficient was used to indicate the correlation between two variables. All *P* values refer to 2-tailed tests of significance and a *P* value of <.05 was considered significant.

3. Results

3.1. Demographic characteristics and contact history

A total of 23 neonates were diagnosed as EV infection with 11 (47.8%) males and 12 (52.2%) females. All of them were born full term. A seasonal pattern of EV infection which occurred between May and September could be observed. Age at presentation ranged from 1 ?to 27 days (median 13, IQR 6–15) with 2 (8.7%) within the first 72 hours of life and 21 (91.3%) after the first 72 hours up to 28 days. Mean body weight was 3510 ± 471 g. Only one of them (4.3%) was admitted to the hospital at birth and the other 22 (95.7%) were from home. History of concomitant fever or upper respiratory tract infection among family members was reported in 11 cases (47.8%).

3.2. Clinical manifestations

All the infants had fever at presentation (100%). The peak temperature during the course ranged from 38.0°C to 39.5°C (median 38.7, IQR 38.3–39.0). The duration of the fever ranged from 1 to 6 days (median 3, IQR 2–4). Another notable symptom was rashes, which occurred in 9 cases (39.1%). The rashes presented as small pink papules densely on the surface of the body and distributed to the soles and palms. Irritability was stated by parents in 6 cases (26.1%). Neither seizures nor abnormal findings in neurological physical examination were reported. None of them had obvious gastrointestinal or respiratory symptoms.

3.3. Laboratory tests

Blood tests and CSF parameters are shown in Table 1.

3.3.1. Changes of complete blood count. Blood WBC count increased in 6 cases (26.1%), whereas normal in the other 17 cases (73.9%). Infants whose blood WBC count increased also had a higher level of neutrophil count ($Z = -2.801$, $P = .005$) and monocyte count ($Z = -2.593$, $P = .010$) compared with those whose blood WBC stayed normal, but the percentage of neutrophil and lymphocyte count did not differ between the 2 groups. Blood WBC count had a significant correlation with

Table 1

Values of blood and CSF tests of the 23 neonates infected by enterovirus.

Laboratory index	Median	Range	IQR
Blood WBC count (cells/μL)	9.06	4.70–22.24	7.29–12.77
Neutrophil count (cells/μL)	4.94	1.37–16.69	3.39–7.70
Neutrophil percentage (%)	58.70	15.30–82.40	40.20–71.20
Lymphocyte count (cells/μL)	2.49	1.06–6.21	1.61–3.27
Monocyte count (cells/μL)	0.70	0.17–2.19	0.40–1.06
Platelet count, (cells/μL)	317	148–668	274–418
Serum C–reactive protein ,mg/L	7.90	0.30–108.40	1.90–19.30
Procalcitonin, mg/L	0.17	0.05–4.71	0.08–0.40
WBC count in CSF (cells/mL)	4	1–635	1–25
Protein in CSF, g/L	0.74	0.55–1.04	0.60–0.86
Glucose in CSF, mg/L	522	432–918	468–594

CSF = cerebrospinal fluid; WBC = white blood cell.

neutrophil count ($r=0.884$, $P<.001$) and monocyte count ($r=0.527$, $P=.010$), but no correlation with lymphocyte count ($0=0.178$, $P=.418$).

3.3.2. Changes of serum CRP and PCT. Serum CRP increased in 10 cases (43.5%), whereas PCT increased in only 4 cases (17.4%). There was a strong correlation between serum CRP and PCT ($r=0.934$, $P<.001$), but no significant correlation was found between serum CRP ($r=-0.040$, $P=.855$) or PCT ($r=0.184$, $P=.401$) and blood WBC count.

3.3.3. Changes of CSF routine and biochemical parameters. CSF WBC elevation (also known as CSF leukocytosis) was observed in 6 cases (26.1%), whereas protein and glucose levels were all within the normal range. Infants with CSF leukocytosis also had a higher level of blood WBC ($Z=-2.731$, $P=.006$) compared with those whose CSF WBC stayed normal, but neither serum CRP nor PCT differed between the 2 groups. Although the elevation of blood WBC tended to be consistent with CSF leukocytosis (Kappa = 0.549, $P=.008$), the correlation between the 2 variables was not significant ($r=.298$, $P=.168$). Neither serum CRP ($r=-0.230$, $P=.292$) nor PCT ($r=-0.147$, $P=.503$) correlated with CSF WBC.

3.3.4. EV nucleic acid detection. All the infants received EV nucleic acid detection of both throat swab and CSF samples. CSF EV was positive in 21 cases (91.3%), also defined as aseptic meningitis, with one CA-16-positive and 20 universal sequence-positive. Throat swab EV was positive in 10 cases (43.5%) with one EV-71 positive and 9 universal sequence-positive. Eight had universal sequence positive both in CSF and throat swab (34.8%). The positive rate of EV nucleic acid in CSF was significantly higher than that in throat swab (91.3% vs 43.5%, $P=.007$).

3.3.5. Laboratory tests of aseptic meningitis. Among 21 aseptic meningitis, 6 had CSF leukocytosis (28.6%), whereas 15 did not (71.4%). Although CSF leukocytosis only occurred in infants with EV positive in CSF, the consistency between CSF leukocytosis and aseptic meningitis did not show significance (Kappa = 0.065, $P=.379$). EV meningitis tended to have a normal blood WBC (Kappa = -0.184, $P=.013$). No significant consistency was found between serum CRP (Kappa = -0.020, $P=.846$) or PCT (Kappa = 0.039, $P=.497$) and meningitis.

3.3.6. Bacterial cultures. Both blood and CSF bacterial cultures were negative in all cases, which did not support bacterial sepsis.

3.4. Brain magnetic resonance imaging findings

Brain magnetic resonance imaging was only performed in 5 infants with obvious CSF leukocytosis, including T1, T2, diffusion-weighted imaging, and enhanced scan. No craniocerebral injuries were found except for meningeal enhancement in 2 cases.

3.5. Treatment and clinical outcome

Empirical antibiotics were administrated in all infants on admission until bacterial infection could be ruled out. Median duration of antibiotic therapy was 8?days (IQR 6–10, range 4–14), which was also equivalent to the length of stay in hospital. The clinicians in our neonatology tended to decide the duration of antibiotic therapy depending on the duration of fever, serum CRP, and CSF WBC count. So infants with CSF leukocytosis received a longer duration of antibiotic therapy compared with those whose CSF cell count was normal ($Z=-3.608$, $P<.001$). The duration of antibiotic therapy exceeded the recommending duration of empirical antimicrobial therapy (compared with 48–72 hours, $P<.001$), but shorter than traditional duration of bacterial meningitis (compared with 14 days, $P<.001$).[16,17] Physical methods were applied for cooling when the infants had a fever. No antipyretics were prescribed. None of the infants was given intravenous immunoglobulin. Neither severe complications nor deaths were recorded.

3.6. Neurodevelopmental outcome at follow-ups

After discharge, 10 of 21 aseptic meningitis were followed up at outpatient clinic (47.6%) and their neurodevelopmental assessment showed normal. Five (23.8%) were followed up through telephone interviews and no obvious neurodevelopmental impairments was detected by their parents.

4. Discussion

In our study cohort, the occurrence of EV infection was concentrated between May to September, which was consistent with the seasonal distribution revealed by other researchers.[19,20] Most of the infections occurred after the first 72 hours of life, which were acquired household mostly indicated horizontal transmission, whereas a few occurred within the first 72 hours of life acquired household mostly, which indicated the possibility of vertical transmission. However, little is known about EV maternal prevalence and risk of transmission.[21] Through a detailed consultation, nearly half of the infections could be traced back to a history of contact with family members who got a cold.

The most common symptom of EV infection in neonates at presentation was fever, followed by rashes. The characteristic rashes which presented on the whole surface of the body particularly on the soles and palms might highly suggest EV infection.[22] Although irritability was reported in some cases, the symptom was more subjective by the parents' narrative as "angry baby." Vomiting, myoclonic twitching, and startle which are more objective are common in infants or children at older ages but scarce in neonates.[23] In case of neonates with fever and typical rashes during the epidemic season, especially to those who had a history contacting family member with a flu, EV infection should be considered in the differential diagnosis.

Previous studies had found out that aseptic meningitis could be caused by EV in children or infants and emphasized the importance of CSF virus nucleic acid detection for diagnosis.[15,23] Meanwhile data on neonates were still limited. Only a few studies involved neonates, which had also shown that EV was an important pathogen in neonatal viral meningitis.[13,24,25] Our study had gathered more infectious cases exclusively in the neonatal period and included complete clinical data of every cases for analysis. Our study revealed a high incidence of aseptic meningitis in neonates infected by EV. However, leukocytosis was only presented in a small proportion of patients in CSF without high protein levels or hypoglycemia. Other related studies also reported an incidence of 36% to 52% of CSF leukocytosis in EV meningitis.[15,23] Our study further confirmed no significant consistency between CSF leukocytosis and aseptic meningitis, consistent with the opinion that CSF leukocytosis was a poor predictor of EV meningitis.[26] However, CSF leukocytosis

cannot differentiate between bacterial and aseptic meningitis.[27] Since obtaining microbial cultures results had a time delay of 2 to 3 days,[27] nearly all infants with CSF leukocytosis hospitalized received broad-spectrum antibiotics while awaiting culture results. Therefore, it is recommended that if a lumbar puncture is conducted in a febrile neonate, CSF EV nucleic acid detection should be obtained as well as routine items and bacterial culture to allow for quick test and early diagnosis of EV infection. However, even EV infection could be confirmed at the very beginning, concomitant bacterial infection should be still considered on some occasions, which also concerns about the duration of antibiotic therapy. Serum CRP and PCT are widely used in the evaluation of neonatal sepsis and guiding the duration of antibiotic therapy. Although the cutoff values varied in different clinical centers, it is recommended that an appropriate cutoff interval of 0.5 to 2 mg/L for PCT and 10 mg/L for CRP to ensure good sensitivity and specificity in the diagnosis of neonatal sepsis.[28] Several studies proposed that two consecutive CRP levels <10 mg/L 24 hours apart, 8 to 48 hours after presentation, has a negative predictive value for sepsis of 99%,[29] which could be used as indications to discontinue antibiotics. Hence, on balancing the unnecessary antibiotic treatment and the fear of missing sepsis, we suggested a combination of PCT and CRP to determine the initiation and the course of antibiotics, rather than CSF leukocytosis in suspected or even confirmed EV infection. However, there is still a lack of well-designed prospective trials to assess the appropriate empirical antibiotic application in suspected EV infection mimicking blood culture-negative sepsis.

There is no effective treatment against EV. Although the pleconaril trial in newborns had shown potential efficacy on increasing survival,[30] the application remains controversial. The treatment for EV infection is more supportive rather than antiviral. Case series reported successful treatment of intravenous immunoglobulin for myocarditis caused by EV.[25] Neither of the 2 therapies was applied in our study cohort involving meningitis exclusively. All the infants recovered well and short-term follow-up revealed no obvious neurologic sequelae.

Although our study showed detailed clinical information of a group of EV infected neonates, it still had some limitations. First it was a retrospective study from a single center with a small sample size, which did not allow further analysis between CSF nucleic acid positive and negative groups. Second the detection of EV acid only included universal sequence and 2 major genotypes (CA-16 and EV-71), lacking comprehensive phylogenetic analysis. Nevertheless, we focused on a rare but emerging disease in neonates, and challenged the rationality of current empirical antibiotic treatment guided by non-specific biomarkers, hoping to provide useful information for better identifying EV infection in clinical work and invoke further study of this disease including epidemiology, subtype analysis, standards for the application of antibiotics, and cohort analysis of long-term prognosis.

5. Conclusion

Aseptic meningitis is a common type of EV infection in neonates with a benign course. Nucleic acid detection of CSF has important diagnostic value in EV infection. Febrile neonates are being suggested to screen for EV infection in addition to complete septic workup. An unnecessary initiation or earlier cessation of antibiotics could be considered in suspected EV infection, but still need further studies to guarantee the safety. PCT and CRP were still useful biomarkers in guiding the application of antibiotics.

Author contributions

Conceptualization: Wen-wen Chen, Liping Xu.
Data curation: Wen-wen Chen, Shu-zhen Dai, Liping Xu.
Formal analysis: Wen-wen Chen, Liping Xu.
Investigation: Wen-wen Chen, Liping Xu.
Methodology: Wen-wen Chen, Shu-zhen Dai, Liping Xu.
Project administration: Wen-wen Chen, Liping Xu.
Resources: Wen-wen Chen.
Software: Wen-wen Chen, Shu-zhen Dai, Liping Xu.
Supervision: Shu-zhen Dai, Liping Xu.
Validation: Liping Xu.
Visualization: Liping Xu.
Writing – original draft: Wen-wen Chen.
Writing – review & editing: Wen-wen Chen.
Xu had primary responsibility for protocol development and outcome assessment. Chen participated in the patient screening, statistical analysis and mainly writing of the manuscript. Dai contributed to data collection and partial writing of the manuscript.

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